The treatment of patients with heart failure is complex and multi-disciplinary, and comprehensive care for these patients integrates established interventions with emerging therapies. Contemporary programs for advanced heart failure need to provide patients with rapid access to novel heart failure therapies when they are approved. After a several-year drought in new therapies, the FDA recently approved three new therapies for heart failure—two drugs and one device.

Sacubitril/valsartan (Entresto™) is a combined neprilysin inhibitor and angiotensin II receptor blocker (Angiotensin Receptor-Nepriysin Inhibitor, ARNI) that is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. Neprilysin degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin raises the levels of these substances, countering the deleterious neurohormonal overactivation that occurs in heart failure. Sacubitril/valsartan was approved based on a single, international trial (PARADIGM HF) that randomized 8,442 patients with NYHA Class II-IV and a left ventricular ejection fraction of ≤40% to receive either enalapril (10 mg bid) or sacubitril/valsartan (200 mg bid). To be randomized, subjects had to complete a single blind run-in phase to demonstrate tolerance to enalapril 20 mg bid and a second single blind run-in phase to ensure an acceptable side effect profile with the ARNI. Excluded subjects were those with a systolic blood pressure <95 mg Hg, history of angioedema, estimated GFR < 30 ml/min, potassium > 5.2 mmol/L, or failure to complete either run-in phase of the trial. Sacubitril/valsartan was associated with a 20% reduction in the primary endpoint of death from cardiovascular causes or hospitalization for heart failure. All-cause mortality was decreased by 16% and cardiovascular mortality by 20%. All subgroups showed a similar benefit. Interestingly, in the OVERTURE trial published in 2002, omapatrilat (a combination of neprilysin inhibitor and an angiotensin-converting enzyme (ACE) inhibitor) failed to show a reduction in the primary endpoint of death or hospitalization for heart failure compared with ACE inhibitor alone. The potentially greater benefit observed with sacubitril/valsartan could be attributable to angiotensin receptor blockade, given the increase in angiotensin II that occurs with neprilysin inhibitors. There is substantial excitement about sacubitril/valsartan because of the significant mortality benefits when added to standard heart failure therapies.

Ivabradine (Corlanor™) inhibits the sinus node If channel to produce a dose-dependent bradycardia without negative inotropy. It is indicated “to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35% who are in sinus rhythm with resting heart rate ≥70 beats per minute and either are on maximally indicated doses of beta-blockers or have a contraindication to beta-blockers.” Because beta-blockers reduce mortality, and the data for reduction in mortality with ivabradine are less certain,
ivabradine should be used only after careful attempts to increase beta blockers have failed to lower the heart rate to < 70 beats per minute.

The approval of ivabradine was based on two large randomized trials (BEAUTIFUL and SHIFT) conducted primarily in Europe.\(^3\)\(^5\) After European approval of this drug, it was widely expected that the FDA would convene a Cardiorenal Advisory panel to consider the drug, but the drug was approved without a full panel discussion. Controversy remains about whether beta-blocker titration was adequately attempted in BEAUTIFUL and SHIFT, and about the safety of the drug in patients with activity-limiting angina and heart failure (due to the results of SIGNIFY). SIGNIFY was a recent, large randomized trial evaluating ivabradine in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of ≥70 beats per minute.\(^6\) Subjects were randomly assigned to placebo or ivabradine, at a dose of up to 10 mg twice daily, with the dose adjusted to achieve a target heart rate of 55 to 60 beats per minute. The primary endpoint was a composite of death from cardiovascular causes or nonfatal myocardial infarction. After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (6.8% and 6.4%, respectively; P=0.20), nor were there significant differences in the incidences of death from cardiovascular disease or nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs. 2.3%, P<0.001).

Ivabradine should not be used in patients taking strong cytochrome P450 3A4 inhibitors, in those with a heart rate < 60 beats per minute, or in those who are pacemaker-dependent.

CardioMEMS Heart Failure System

In May 2014, the FDA approved the CardioMEMS™ Heart Failure System “to reduce heart failure readmissions in patients with chronic heart failure.” The system became available in fall 2014, and has been clinically available since then. The system consists of an implantable pulmonary artery...
(PA) sensor, delivery system, and Patient Electronics System. The implantable sensor is permanently placed in the pulmonary artery during an outpatient right heart catheterization procedure. Patients must be able to take aspirin and clopidogrel (Plavix) for one month following implantation. The PA sensor is about the size of a small paper clip and has a thin, curved wire at each end (Figure 1). The sensor does not require any batteries or wires. The Patient Electronics System includes the electronics unit, antenna, and pillow. The patient lies down on a pillow each day to wirelessly transmit PA pressures which are then downloaded by health care providers. The pattern of increases (or decreases) in PA pressures allows health care providers to adjust medications to normalize PA pressures with diuretics or vasodilators.

After an FDA panel rejection of CardioMEMS in December 2011, a second FDA advisory committee in early 2014 narrowly recommended approval (6 votes to 4). The approval was based largely on an open-label study conducted with patients enrolled in the CardioMEMS pivotal trial (CHAMPION). In the CHAMPION study, the PA pressure sensor was implanted in 550 NYHA class III heart-failure patients (both reduced and preserved ejection fraction) with a history of decompensation. Control subjects had the device implanted but pressures were not transmitted to health care providers. The system was associated with a 30% reduction in hospitalizations compared with standard care. There was a 39% reduction in heart-failure-related hospitalization in the treatment group compared with the control group at 6 months.

The CardioMEMS System is now available at Vanderbilt. For questions or evaluation of patients for the CardioMEMS system please contact Connie Lewis, N.P., Kelly Schlendorf, M.D., Daniel Lenlihan, M.D., or JoAnn Lindenfeld, M.D. Patients implanted with the CardioMEMS device will be monitored by the Heart Failure team.

References: