New Evidence: Treatment of Heart Failure

Written by Lori Alexander

The European Society of Cardiology (ESC) updated its guidelines on the diagnosis and treatment of acute and chronic heart failure (HF) in May 2012 [McMurray JJV et al. *Eur Heart J* 2012]. Updates to the guidelines include recommendations for new medical therapies and recognition of the growing use of ventricular assist devices (VAD); research continues in both of these areas to identify optimal management. In addition, efforts continue to address the best approach to patient monitoring.

Patient Monitoring

The trajectory in patients with HF is unpredictable, marked by periods of crises, said Martin R. Cowie, MD, National Heart and Lung Institute, Imperial College, London, United Kingdom. Adding to the challenge of treatment is that "usual care" consists of brief periodic office visits, with decisions made with little information. Structured telephone support and remote monitoring offer the potential for gathering more data to inform decision-making, but the ESC guidelines do not strongly support monitoring and technology. In addition, questions remain about the most effective use of data obtained from remote monitoring.

Some studies have demonstrated no differences in outcomes between patients who were monitored remotely and those who were not. However, some of these studies used outdated technology that was not user-friendly. A significant benefit for the use of both structured telephone support and telemonitoring was found in a recent meta-analysis, with reductions in all-cause mortality, HF-related hospitalizations, and cost as well as improved quality of life (QoL) [Inglis SC et al. *Eur J Heart Fail* 2011]. Current ESC Guidelines state that the evidence is not robust enough to recommend such systems, noting that telephone support and telemonitoring are "possible" approaches for follow-up.

One of the largest studies on telemonitoring is the Whole System Demonstrator (United Kingdom), which involves more than 6000 patients who have HF, chronic obstructive pulmonary disease, or diabetes [Steventon A et al. *BMJ* 2012]. The data have not been fully analyzed yet, but Prof. Cowie reported that the preliminary results include a 15% reduction in emergency room visits, a 21% reduction in emergency room admissions, a 14% reduction in elective admissions, a 14% reduction in bed days, and a 8% reduction in tariff costs (mandatory and indicative tariffs used in United Kingdom for the reimbursement of inpatient and outpatient care).

Guideline recommendations are not yet possible for implanted monitoring devices either. Such devices provide a great deal of data, and finding a single parameter to monitor has been a challenge. Treatment decisions will require making intelligent interpretations of several different markers. Indicators of possible HF decompensation have included changes in heart rate variability, night heart rate, and patient activity.

Future guidelines should include stronger statements about technology and how to integrate monitoring data into decision-making, said Prof. Cowie. In addition, guidelines should address the answers to important questions: How should the data be presented, how often, and to whom?

New Medical Therapies

In addition to standard recommended drugs for HF (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [ARBs], β-blockers, and mineralocorticoid receptor antagonists [MRAs] for persisting symptoms), direct renin inhibitors, vasodilating neurohormones, new inotropes, and heart rate modulators offer potential as new treatments for HF, said John R. Teerlink, MD, University of California, San Francisco, San Francisco, California, USA.

The 2 MRAs most widely studied are spironolactone and eplerenone. When added to conventional treatment, spironolactone has been to shown to reduce mortality and hospitalizations in patients with advanced HF. A trial of spironolactone compared with placebo for diastolic HF showed no change in peak oxygen consumption during exercise or in QoL [Pieske BM et al. 2012 ESC Hot Line; see page 14 of this report]. Eplerenone was evaluated in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure [EMPHASIS-HF] trial, which was stopped early for significant benefit [Zannad F et al. *N Engl J Med* 2011]. The primary outcome, a composite of death from cardiovascular (CV) causes or hospitalization for HF, occurred in significantly fewer patients receiving eplerenone (18.3%) than those receiving placebo (25.9%; $p<0.001$). Hospitalizations for HF or any other cause were also reduced with eplerenone.

Hyperkalemia is a primary problem with MRAs. A novel non-steroidal MRA, BAY 94-8862, has greater selectivity than spironolactone and stronger MRA binding affinity

than eplerenone. This agent drug is being evaluated to determine its safety and efficacy, with serum potassium levels as one outcome measure [NCT01345656].

Aliskiren is the first orally active direct renin inhibitor, and it has been evaluated in several studies, including comparisons with placebo, with enalapril monotherapy and in combination with enalapril [Gheorghiade M et al. *Eur J Heart Fail* 2011; Krum H et al. *Eur J Heart Fail* 2011]. Dr. Teerlink noted that aliskiren was found to be associated with an increased risk for adverse events in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints [ALTITUDE] trial, which involved patients with type 2 diabetes at high risk for CV and renal events [Parving HH et al. 2012 ESC Hot Line; see page 13 of this report].

Among the vasodilating neurohormones being evaluated as treatment for HF is LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, which led to significant improvement in N-terminal prohormone brain natriuretic peptide in the Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction [PARAMOUNT] trial [Solomon SD et al. *Lancet* 2012; see page 11 of this report]. LCZ696 is being compared with enalapril in the ongoing Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients with Chronic Heart Failure [PARADIGM-HF; NCT01035255] trial.

Relaxin is a vasoactive neurohormone that has been shown to relieve dyspnea and improve congestion and possibly decrease 60-day mortality or HF-related hospitalization [Teerlink JR et al. *Lancet* 2009]. Updated results of the Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure [RELAX-AHF; NCT00520806] trial are scheduled to be presented at the American Heart Association Scientific Sessions in November 2012.

New inotropes in development are stresscopin; CXL-1020, a nitroxyl donor; and omecamtiv mecarbil, a myosin activator. More studies are needed to determine the safety and efficacy of these drugs for patients with HF.

The heart rate modulator ivabradine significantly reduced risk (18%; $p<0.0001$) of CV death or hospitalization for worsening HF, in patients with symptomatic HF (NYHA class II-IV) and LVEF ≤35%, who were in sinus rhythm with a heart rate ≥70 beats per minute [Swedberg K et al. *Lancet* 2010]. Dr. Teerlink noted that treatment with a β-blocker should be maximized before treatment with ivabradine is started.

Ventricular Assist Devices

Only a fraction of patients eligible for a left ventricular assist device (LVAD) receive one, said Antonios Pitsis, MD, Thessaloniki Heart Institute, Thessaloniki, Greece. However, improved outcomes with later generation devices and the United States Food and Drug Administration approval of the HeartMate II as destination therapy have increased the number of destination therapy implantations 10-fold since January 2010.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure [REMATCH] trial was the first study to compare an assist device with medical therapy, and the device led to a doubling of 1-year survival (from 25% to 52%) [Rose EA et al. *N Engl J Med* 2001]. Newer continuous-flow devices have been associated with better 2-year survival and lower rates of disabling stroke and reoperation than with pulsatile-flow devices [Slaughter MS et al. *N Engl J Med* 2009], as well as with clinically relevant improvements in functional capacity and HF-related QoL [Rogers JG et al. *J Am Coll Cardiol* 2010]. According to the Fourth Annual Report of the Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] annual report, the current actuarial survival with continuous-flow devices was 82% at 1 year and 74% at 2 years, compared with 61% and 43%, respectively, for pulsatile-flow devices [Kirklin JK et al. *J Heart Lung Transplant* 2012]. When used as destination therapy, the devices are associated with a 1-year survival rate of 74%.

Defining patient profiles with regard to severity of disease is important when considering the use of an LVAD, and INTERMACS has categorized patients into 7 levels from "crash and burn" to advanced class III. Among the significant risk factors for death with destination therapy are an older age, critical cardiogenic shock, diabetes, pulmonary hypertension, high BUN level, low sodium level, concomitant surgery, use of a bi-VAD, and use of a pulsatile-flow device.

Prof. Pitsis said that attempts are being made to implant VADs earlier, but he expressed caution about this approach until the results of the Randomized Evaluation of VAD Intervention Before Inotropic Therapy [REVIVE-IT; NCT01369407] trial are available. He added that patients with biventricular failure are still better treated with urgent heart transplantation.

Better patient selection, management approaches, and technical advances will help to improve outcomes and decrease adverse events. Future efforts include further miniaturization of devices to allow for less invasive implantation, wider implementation of newer technologies to reduce anticoagulation, and partial support for patients with class IIIb disease who are exercise intolerant. Prof. Pitsis added that patients want a fully implantable device, and one should be available in the coming years.