

Drugs, Devices Differ for Two Heart Failure Types

BY ALICIA AULT

Associate Editor, Practice Trends

BALTIMORE — With at least six drugs and several devices to choose from for heart failure, it's important to approach asymptomatic and symptomatic patients differently, Dr. Edward Kasper said at a cardiovascular conference sponsored by Johns Hopkins University.

Dr. Kasper bases his treatment decisions on the 2005 guidelines from the American College of Cardiology and the American Heart Association for the diagnosis and management of chronic heart failure in adults (*J. Am. Coll. Cardiol.* 2005;46:e1-82).

For asymptomatic patients, the evidence is strong that ACE inhibitors reduce mortality, said Dr. Kasper, chief of cardiology at Johns Hopkins Bayview Medical Center, Baltimore. The best data come from the Studies of Left Ventricular Dysfunction (SOLVD) trial (*N. Engl. J. Med.* 1992;327:685-91) and from a separate long-term follow-up of the patients that found that

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after 12 years, 50.9% of those taking enalapril had died, versus 56.4% of those taking placebo (*Lancet* 2003;361:1843-8).

The data are not as clear for angiotensin receptor blockers or β -blockers in asymptomatic patients. Post-MI, both β -blockers and ACE inhibitors reduce mortality, Dr. Kasper said.

For primary prevention in asymptomatic patients with ischemic cardiomyopathy and an ejection fraction of less than 30%, implantable cardioverter defibrillators (ICDs) are the best choice, as shown in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). Patients were randomly assigned to a defibrillator or conventional medical therapy. The death rate was substantially lower for the ICD group—14%, compared with 20% for medical therapy. The results do not apply to nonischemic myopathy, he said.

For symptomatic patients, the first line is diuretics and restricted salt intake. β -Blockers and ACE inhibitors are also employed. Dr. Kasper cautioned against using NSAIDs for gout, noting that the drugs can worsen the heart failure. Most antiarrhythmics are contraindicated for the same reasons, Dr. Kasper said.

The main data backing ACE inhibitors in symptomatic patients come from the treatment arm of the SOLVD trial, and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I) (*N. Engl. J. Med.* 1987;316:1429-35). Mortality was substantially reduced in both. The exact ACE inhibitor is not important, Dr. Kasper said. But the choice of β -blocker is important, he said. A study in 2003 in 3,029 patients with New York Heart Association class II-IV heart failure and an ejection

fraction of less than 35% were randomized to 25 mg of carvedilol twice daily or 50 mg of metoprolol tartrate (Lopressor) twice daily. With a mean follow-up of 58 months, the all-cause mortality was 34% in the carvedilol group, compared with 40% in the metoprolol group (*Lancet* 2003;362:7-13).

Dr. Kasper said he generally uses carvedilol in new patients and either carvedilol or metoprolol succinate (Toprol XL) in established patients. Both drugs

have been approved for the treatment of chronic heart failure.

For ICDs, the guidelines suggest implantation for class II or III patients who have an ejection fraction of less than 30%; patients with ischemic cardiomyopathy should be at least 40 days post MI. The primary data supporting a reduction in mortality come from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (*N. Engl. J. Med.* 2005;352:225-37). Implant candidates should have a life ex-

pectancy of at least a year, Dr. Kasper said.

Pacemakers should be considered in class III or IV patients who have an ejection fraction of less than 35% and a history of hospitalization or medical therapy, he said. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study showed that biventricular stimulation with or without an ICD reduced the risk of death and hospitalization (*N. Engl. J. Med.* 2004;350:2140-50). ■

CRITICAL INSIGHTS INTO THE NATURE OF NICOTINE ADDICTION

A SUMMARY OF KEY LEARNINGS TO DATE

With all the public awareness efforts that have been made, and with all the truths that have come to light over the last several decades about the dangers of smoking, one obvious question lingers: **Why are people still smoking?**

Understanding nicotine addiction

Most experts agree at this point that smoking is a chronic, relapsing condition—an addiction similar in nature to that seen in cocaine and heroin users.^{1,2} Following are 4 criteria the Surgeon General has used to define addiction, along with an explanation of how nicotine—specifically smoking—meets these criteria.²

1. Addiction leads to compulsive use, despite adverse consequences

According to a 1988 Surgeon General's report, "highly controlled or compulsive use indicates that drug-seeking and drug-taking behavior is driven by strong, often irresistible urges. It can persist despite a desire to quit or even repeated attempts to quit."² Smoking statistics show that approximately **70% of current smokers report that they want to quit**; however, only about 5% of smokers who try to quit without medical aid succeed.^{3,4} In fact, the average smoker has tried to quit **6 to 9 times**.⁵ It is common for people to continue smoking despite known negative health consequences. In fact, smoking behavior often persists even after the presentation of comorbid conditions.^{2,6,7}

2. Addiction involves a psychoactive substance with reinforcing properties

The psychoactive (mood-altering) properties of nicotine are substantially related to its effect on the mesolimbic dopaminergic system. For delivery of nicotine, smoking is the most efficient mechanism. In a matter of seconds, nicotine from inhaled smoke crosses the blood-brain barrier and begins altering brain chemistry through binding to

cholinergic receptors normally activated by acetylcholine. Dopamine is released in the nucleus accumbens, triggering central nervous system effects such as pleasure, relief of anxiety, better task performance, and improved memory. These rewards serve to reinforce smoking behavior.^{2,8-10}

Complicating this effect is that the routines associated with smoking, such as smoking in social environments, can also come to be reinforced through the pleasure response. Eventually, the pleasure associated with smoking in these settings acts as a subconscious trigger, making it hard for the smoker to dissociate the behavior from the addiction. **This explains why successful quit attempts often require some degree of behavioral modification.**^{2,11,12}

3. The addicted subject develops tolerance

Nicotine initiates its action by competitively binding at the nicotinic acetylcholine receptors (nAChRs), ligand-gated ion channels on the cell membrane. Compared with the endogenous agonist acetylcholine, nicotine causes a prolonged activation of nAChRs. The activation is followed by a desensitized state in which the receptors are unresponsive to agonists. This process has been compared to tripping a circuit breaker.^{10,11,13}

Chronic use of nicotine leads to chronic desensitization of nAChRs. As more nicotine is consumed, and more receptors become desensitized, **the user experiences a diminished pleasure effect with each subsequent cigarette smoked.** As the response decreases, increasing levels of nicotine are required to achieve a consistent, desired effect.^{2,10-12} These are defining characteristics of tolerance.¹⁴

