New Drugs Give New Ways to Treat, Prevent AF

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BOSTON — New drugs for treating or preventing atrial fibrillation are coming from new ways to change the electrical properties of the atria and promote sinus rhythm.

The new agents differ from the approved antiarrhythmic drugs for atrial fibrillation (AF)—such as dofetilide—which also affect ventricular rhythms and cause adverse effects. New drugs target different ion-channel effects, have multiple ion effects, or work by a mechanism that does not involve ion channels, Dr. Peter Kowey said at an international symposium on atrial fibrillation sponsored by the Academy of Healthcare Education.

▶ **Azimilide.** This agent acts by blocking both rapid and slow potassium channels in myocardium, and is chemically distinct from other class III antiarrhythmic drugs like sotalol, amiodarone, and dofetilide. After many long-term studies, including phase III trials, the development of azimilide for preventing AF recurrence was dropped, despite clear evidence of efficacy, because it did not look potent enough, said Dr. Kowey, professor of medicine at Jefferson Medical College, Philadelphia, and president of the Main Line Health Heart Center at Lankenau Hospital, Wynnewood, Pa. Azimilide is under review by the Food and Drug Administration for patients with implantable cardioverter defibrillators for the indication of preventing new device events in patients with frequent events.

▶ **Tedisamil.** Study results showed that tedisamil, which blocks all potassium channels, is more effective than placebo for stopping AF. Despite the possibility that it can cause torsades de pointes, the drug remains in development because it's especially effective for stopping AF that's lasted for days or even weeks; available drugs are primarily effective only when the AF has been going on for hours.

▶ **Dronedarone.** Now under FDA review, dronedarone is an amiodaronelike compound that lacks the iodine moiety and is safer than amiodarone. Safety data from phase III efficacy trials showed that dronedarone lacked the pulmonary and thyroid toxicity of amiodarone, and it clearly prolonged the time to first recurrence of AF. But results from the ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) study, which studied the drug in patients with heart failure and AF, linked dronedarone treatment with an excess of deaths from heart failure. This indication of a problem led to the ATHENA (A Trial with Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation) study; it enrolled 3,700 patients who may not have been as sick as those in ANDROMEDA. Results from ATHENA are expected next year, and will determine the FDA's future review of the drug.

▶ **Vernakalant.** Formerly known as RSD-1235, this is the first "atrial-selective" drug to reach the FDA for review. This IV drug seeks labeling for terminating AF in patients with arrhythmia of "relatively recent onset." Results from phase III studies, especially the ACT III trial, showed that vernakalant was effective for converting patients to sinus rhythm when AF lasted for a week or less. An oral formulation showed efficacy for preventing new AF episodes in one phase II study, with a safety profile that was similar to placebo, but only 171 patients were included. Although vernakalant and other drugs in the class have a reduced ventricular effect, increasing the dosage does produce greater ventricular effects.

▶ **Gap junction modulators.** These agents, a new class of AF drugs, are thought to work by restoring intercellular connections that may be arrhythmogenic when malfunctioning. Preclinical development has so far not identified a good candidate for clinical testing. In trials with other end points, the angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have been linked with reduced frequency of AF in empirical observations and post hoc analyses, which warrants the running of studies designed to directly test the drugs' antiarrhythmic efficacy. Anti-inflammatory agents, such as statins and polyunsaturated fatty acids, have also shown hints of reducing AF incidence.

For many new agents for stopping or preventing AF, a trial to measure the time to first recurrence of symptomatic AF is irrelevant, so new ways to test them need to be designed, Dr. Kowey said. ■