ARRHYTHMIAS

RAAS inhibition in atrial fibrillation—one strike, but not out?

Inhibition of the renin–angiotensin–aldosterone system is a potential strategy to reduce morbidity and mortality associated with atrial fibrillation (AF). The placebo-controlled Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE I) was designed to investigate the effects of the angiotensin-receptor blocker (ARB) irbesartan in this setting. The results of this study have now been published in the *New England Journal of Medicine*. Disappointingly, irbesartan was found not to reduce the incidence of the two primary composite end points (stroke, myocardial infarction, or vascular death, and stroke, myocardial infarction, vascular death, or hospitalization for heart failure) among patients with AF. “Despite the negative main results, there were encouraging and significant reductions in key secondary outcomes,” reports Dr Jeff Healey, one of the ACTIVE I investigators.

Considerable interest exists in developing treatments to target the underlying causes of AF. Hypertension is a major risk factor for this condition and several studies have indicated that blood-pressure-lowering agents, such as ARBs and angiotensin-converting-enzyme (ACE) inhibitors, could ameliorate electrical remodeling in the atria and prevent AF. In addition, “strategies that can prevent intracranial hemorrhage and heart failure are needed,” explains Dr Healey. These outcomes are not

prevented by current anticoagulant-based and antiplatelet-based therapy.

The study population for ACTIVE I were drawn from the cohorts of two earlier trials (ACTIVE W and ACTIVE A) that assessed the effects of oral anticoagulation versus clopidogrel plus aspirin or clopidogrel plus aspirin versus clopidogrel alone, respectively, in patients with AF. Patients enrolled in either of these trials, who had a systolic blood pressure ≥ 110 mmHg were also eligible for inclusion in ACTIVE I. Participants were randomly assigned to receive placebo ($n=4,498$) or irbesartan 150 mg per day for 2 weeks followed by 300 mg per day for the remainder of the study ($n=4,518$). At baseline, 60% of patients in each group were already taking ACE inhibitors, 62% were receiving antiplatelet agents, 38% were taking oral anticoagulants, and 23% were receiving antiarrhythmic drugs. The majority of patients (76%) were in AF at enrollment, and 19% were in sinus rhythm.

During follow-up (mean 4.1 years), a trend toward greater blood-pressure reduction with irbesartan was reported when compared with placebo (mean systolic/diastolic reduction: 6.8/4.5 mmHg for irbesartan vs 3.9/2.6 mmHg for placebo). The incidence of the co-primary outcomes did not differ significantly between the two groups. However, significantly fewer first hospitalizations for heart failure were reported in the irbesartan group than in the placebo group

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(482 vs 551; $P=0.02$) and fewer patients receiving irbesartan were hospitalized for any cardiovascular event (3,817 vs 4,060; $P=0.003$). In addition, trends towards lower rates of stroke, transient ischemic attacks, and systemic emboli were noted with irbesartan therapy. More patients taking irbesartan discontinued treatment than those receiving placebo (for symptomatic hypotension 127 vs 64, $P<0.001$; for renal dysfunction 43 vs 24, $P=0.02$).

Although “these results do not support the routine use of irbesartan in patients with AF ... the issue of aggressive blood-pressure control in [these] patients remains an open question,” concludes Dr Healey.

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