Valsartan Cut Cardiovascular Events by 45% 

BY BRUCE JANCIN

BARCELONA — Add-on valsartan for control of high-risk hypertension resulted in a highly significant 45% reduction in the incidence of the primary cardiovascular end point compared with non–angiotensin receptor blocker add-on therapy in the randomized Kyoto Heart Study.

The estimated number of patients who would need to be treated (NNT) with valsartan (Duovas) instead of an alternative antihypertensive drug for 3.27 years to prevent one additional adverse cardiovascular event was 21, Dr. Hiroaki Matsubara noted, Dr. Matsubara is professor of internal medicine at Kyoto (Japan) Prefectural University.

The Kyoto Heart Study randomized 3,042 hypertensive Japanese patients at high cardiovascular risk to open-label add-on valsartan or non-ARB antihypertensive therapy. High risk was defined by the presence of diabetes, ECG evidence of left ventricular hypertrophy, obesity, smoking, or a history of coronary artery disease. With add-on therapy, patients achieved identical blood pressure lowering, going from a mean baseline of 157/88 mm Hg to 133/76 mm Hg. Although the target dose for valsartan was 160 mg/day—the maximum in Japan—the average dose was 88 mg/day.

The trial was halted early, after a median 3.27 years of follow-up, for ethical reasons because the combined primary end point had been reached by 10.2% of control patients, compared with 5.5% of those in the valsartan group. There were 25 strokes in the valsartan arm, compared with 46 in controls. Moreover, the valsartan group had 22 cases of angina pectoris, as determined by a blinded end point committee, compared with 44 cases in the controls. The NNT to prevent one stroke was 72; the NNT to prevent one case of angina was 69.

New-onset diabetes, a prespecified secondary end point, occurred in 86 controls, compared with 58 valsartan-treated patients, which was a highly significant difference.

However, rates of MI, heart failure hospitalization, and all-cause mortality were not significantly different in the two treatment arms.

The Kyoto Heart Study was undertaken because of a dearth of clinical trial data on the use of ARBs in Asian patients. For example, Asians comprised less than 4% of participants in the landmark Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) and Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trials.

The 45% decrease with valsartan was driven by risk reductions of 55% for stroke and 49% for angina.

In the valsartan group was driven chiefly by reductions of 55% in the risk of stroke and 44% for angina, noted Dr. Matsubara and Dr. Ruschitzka reported having analyzed the relation between extent of LDL cholesterol lowering and AF risk. The two proved unrelated, meaning the protective effect involved some statin property other than lowering.

“The effect of rosuvastatin was not overwhelming,” observed discussant Dr. Harry J.G.M. Crijns. “Statin are not very effective in my mind for preventing atrial fibrillation in patients with class IIb-IV heart failure.”

He called AF and heart failure “an insufferable odd couple.” Patients with heart failure have an increased likelihood of developing AF. When it worsens their heart failure and causes strokes. Antiarrhythmic agents are contraindicated in the setting of heart failure, so there is a great need for drugs that will work “upstream”—that is, on the aberrant substrate that gives rise to AF.

The most plausible mechanism by which statins prevent AF is by reducing atrial fibrosis. Statins have been shown to do so in animal studies. But statin therapy that is delayed until patients have advanced heart failure, as in GISSI-HF, is likely too late to have a robust effect because the atrial remodeling is too extensive.

If this hypothesis is correct, starting statin therapy further upstream, when patients have only a short history of heart failure and limited atrial remodeling, should result in a greater anti–atrial fibrillation benefit than seen in GISSI-HF, said Dr. Crijns of Maastricht (the Netherlands) University.

He added that the primary outcome of future studies of statins for prevention of AF in heart failure should be the total AF burden—that is, the cumulative time patients spend in AF—rather than the incidence of the rhythm. There is evidence to suggest total burden is more important from the standpoint of stroke risk.

It’s also important to recognize that it has never actually been shown that patients with heart failure will improve their cardiovascular morbidity and mortality, Dr. Crijns added. That’s widely assumed to be the case, but it’s entirely possible that AF in these patients is simply a marker for a constellation of risks.

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