

# 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 (Diovan) instead of an alternative antihypertensive drug for 3.27 years to prevent one additional adverse cardiovascular event was 21, Dr. Hiroaki Matsubara reported at the annual congress of the European Society of Cardiology.

The combined primary end point consisted of stroke, MI, angina, hospitalization for heart failure, coronary revascularization, renal failure, or peripheral artery disease. The overall 45% decrease in the valsartan group was driven chiefly by reductions of 55% in the risk of stroke and 49% for angina, noted Dr. Matsubara of 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. Al-

though 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 on the basis of ECG evidence and confirmatory coronary angiography, compared with 44 cases in 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 Anti-hypertensive Long-Term Use Evaluation (VALUE) trials, Dr. Matsubara noted.

Cardiovascular disease in the Japanese population differs from that in the United States and Europe.

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DR. MATSUBARA

Japanese have a lower average body mass index than do Americans, but their salt intake is 2.5-fold greater. Calcium channel blockers account for more than 60% of all antihypertensive prescriptions in Japan.

The Kyoto findings suggest valsartan may be considered a vascular-specific ARB. It has the greatest selectivity of any ARB for the angiotensin type-1 receptor, and it appears to be particularly useful in treating hypertensive patients who have angina or who are at risk for stroke, according to Dr. Matsubara.

Discussant Frank Ruschitzka called the 45% reduction in the combined cardiovascular end point with valsartan “almost too good to be true,” pointing to the lack of benefit shown for acute MIs.

And the 49% reduction in angina was unpersuasive: “Angina is a weak end point ... of minor importance,” said Dr. Ruschitzka of the University of Zurich.

He noted that the Kyoto finding that valsartan provided significant protection against stroke but not against MI is consistent with a just-completed meta-analysis he performed with American coinvestigators Dr. Franz H. Messerli and Dr. Sripal Bangalore. The meta-analysis incorporated 26 randomized non-heart failure clinical trials of ARBs totaling roughly 100,000 patients. It showed that ARBs resulted in a significant 13% relative risk reduction for stroke along with a nonsignificant 3% increased risk of MI. In contrast, ACE inhibitors have a well-established protective effect against MI.

“For me, ACE inhibitors and calcium antagonists are my first choice in treating high-risk hypertension. The ARBs are for those who don’t tolerate the ACE inhibitors so well, although clearly they’re equally effective for blood pressure lowering,” the cardiologist concluded.

A more charitable opinion of ARBs for treatment of hypertension was offered by American College of Cardiology President Alfred A. Bove in an interview.

“In hypertension, getting the patients to take their medication is the most important thing you can do. I always say that any drug I can get the patient to take is the right medication. A lot of us like to use ARBs because they have minimal side effects,” said Dr. Bove, a cardiologist at Temple University, Philadelphia.

The Kyoto Heart Study was funded by Kyoto Prefectural University. Dr. Matsubara and Dr. Ruschitzka reported having no financial conflicts of interest regarding their presentations. ■



# Statin Is Mildly Protective Against Atrial Fib in Heart Failure

BY BRUCE JANCIN

BARCELONA — Rosuvastatin exerted a “modest” preventive effect against the occurrence of atrial fibrillation in patients with chronic heart failure, according to a secondary analysis of the Italian GISSI-Heart Failure study.

GISSI-Heart Failure (GISSI-HF) was a double-blind, placebo-controlled trial that randomized 4,574 patients with New York Heart Association (NYHA) class II-IV heart failure to fish oil capsules and/or rosuvastatin at 10 mg/day. The primary outcomes were reported last year (Lancet 2008;372:1223-30, 1231-9).

The new post hoc analysis involved the 3,690 participants without atrial fibrillation (AF) on their baseline ECG. The study showed that during a median 3.7 years of follow-up, 16.0% of the placebo group and 13.9% on rosuvastatin (Crestor) developed AF.

This absolute 2.1% difference translated into a 13% relative risk reduction in the incidence of AF in rosuvastatin-treated patients, which achieved narrowly statistical significance after adjustment for potential confounders, Dr. Aldo P. Maggioni said at the annual congress of the European Society of Cardiology.

On the basis of the GISSI-HF results, 47 patients with moderate to severe heart failure would have to receive

rosuvastatin for nearly 4 years to prevent one case of AF.

However, the observed “modest” beneficial effect may underestimate the true benefit to be derived from longer treatment, since the event curves for rosuvastatin and placebo diverged progressively over the course of the study, noted Dr. Maggioni of the GISSI-HF Coordinating Center in Florence, Italy.

The mild preventive effect was consistently seen in all prespecified subgroups regardless of patient age, ejection fraction, heart failure etiology, renal function, NYHA class, or the presence of diabetes.

In search of the mechanism of benefit, Dr. Maggioni and coinvestigators analyzed the relationship between extent of LDL cholesterol lowering and AF risk. The two proved unrelated, meaning the protective effect involved some statin property other than lipid lowering. “The effect of rosuvastatin was not overwhelming,” observed discussant Dr. Harry J.G.M. Crijns. “Statins are not very effective in my mind for preventing atrial fibrillation in patients with class II-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 they do, 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.

**There was a 13% relative risk reduction in the incidence of AF in rosuvastatin-treated patients.**

DR. MAGGIONI



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 arrhythmia. 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 established that prevention of AF in 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 worse prognosis, and that suppressing the arrhythmia may kill the messenger without squelching the associated risks.

Dr. Maggioni disclosed receiving research support and honoraria from AstraZeneca, which funded GISSI-HF. Dr. Crijns did not disclose any industry relationships. ■