

## Exploring the Benefits Beyond Blood Pressure Control

*Based on presentations by Hans Lithell, MD; and Luis Ruilope, MD*

### **Presentation Summary**

The establishment of strong links between blood pressure and the development of dementia among the elderly is presented. This association is especially important in the hypertension treatment arena because the aging population will produce more dementia-related illness during the coming decades. The most important point discovered so far is that the vascular effects of high blood pressure may be causative in certain types of dementia. Now, a large study is being undertaken to determine whether angiotensin receptor blockade can help prevent the cognitive decline seen in many elderly patients.

The renal effects of high blood pressure are well known but are

most important in the special situations of concomitant heart failure or diabetes. The mechanisms causing renal problems in these patients are identified and the role of angiotensin II is explored. Ongoing studies are expected to show that angiotensin II antagonism may be beneficial in these patient populations.

The cases of dementia and renal disease serve to demonstrate that blood pressure control can benefit other crucial biological systems. Furthermore, it appears that treatments currently available for hypertension may offer benefits extending beyond simple blood pressure control, and through angiotensin receptor blockade, may affect these systems more directly.

**A** number of comorbid conditions have been associated with high blood pressure, and one of the newest among them is dementia. New research has indicated that vascular disease may be a strong component in the development of non-Alzheimer's dementia in the elderly, and of course, hypertension is known to cause vascular disease. Study has now turned toward defining the role of angiotensin II and its blockade in dementia development and prevention.

### **The Dementia Link**

Dementia is a very prevalent problem, and it is estimated that as many as half of people worldwide aged 85 to 90 years suffer from some type of mild to severe dementia. Previously, most dementia cases were attributed to Alzheimer's disease, which has a strong genetic component. However, new information revealed during the last few years has refuted the dominance of the Alzheimer's disease etiology.

For example, a Swedish study involving autopsies of more than 175 patients who had died with the main diagnosis of dementia showed that 71% of patients had signs of a vascular component. The cerebrovascular pathology noticed in these patients included 18% with large vessel disease, 40% with small vessel disease, 22% with both large and small vessel involvement, 38% with white matter arterial stenosis with hypoperfusion, and 3% with hemorrhagic stroke.<sup>1</sup>

"It may well be that vascular disease is one of the reasons for development of dementia in many of the patients," said Hans Lithell, MD, professor, department of geriatrics at the University of Uppsala, Uppsala, Sweden. "Of particular interest is the incidence of white matter arterial stenosis with hypoperfusion. This hypoperfusion may be related to low blood pressure which is very common in elderly patients with dementia." What has been unclear is whether low blood pressure is primary and causes dementia or whether low blood pressure is secondary to the sensory deprivation, weight loss, sedentary life style, and reduced sympathetic outflow of dementia, Dr. Lithell added.

#### Recent Evidence

A milestone was reached with the completion of one Swedish study that partially answered this question. Patients 85 years of age who had white matter lesions documented by computed tomography and who were demented at this time had low blood pressure. However, they had suffered from hypertension from 5 to 15 years earlier. In contrast, patients without white matter lesions and dementia had a history of normal blood pressure during the preceding 15 years.<sup>2</sup>

In order to determine whether high blood pressure was related to later cognitive function, not just dementia, Dr. Lithell and colleagues studied 1000 70-year-old Swedish patients between 1991 and 1995 to evaluate cognitive function using the Mini-Mental State Examination (MMSE). Twenty-four-hour blood

pressure measurements were also recorded, and patients with the lowest diastolic blood pressures scored best on cognitive functions. Those with the highest diastolic pressures scored lowest. Systolic blood pressure below 120 mmHg was associated with the best cognitive functioning while systolic pressure above 140 mmHg was associated with the worst cognitive skills, Dr. Lithell said. Furthermore, patients with the lowest cognitive function scores also tended not to experience blood pressure dipping during the 24-hour measurement.

#### SCOPE Design

Based on this recent research, a secondary aim of the Study on Cognition and Prognosis in the Elderly (SCOPE) study will be to evaluate whether hypertension treatment with an angiotensin II receptor blocker will help prevent a rapid decline in cognitive function among elderly, nondemented, mildly hypertensive patients. "In addition to lowering of blood pressure, a specific effect of angiotensin<sub>1</sub> (AT<sub>1</sub>) receptor blockade may be to improve the structure and function of small vessels, thereby influencing dementia development," Dr. Lithell explained.

The primary goal of SCOPE is to study whether treatment of very mild hypertension in quite elderly patients will prevent cardiovascular disease, and the main endpoints are major cardiovascular events. Secondary endpoints in addition to cognitive function will include quality of life and health economics outcomes, total mortality, cardiovascular mortality, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and impaired renal function.

SCOPE is a placebo-controlled, parallel group study with patients being randomized after a 2-month washout period to either active treatment with candesartan cilexetil or placebo for a mean treatment duration of 2.5 years. It will eventually include 4000 patients aged 70 to 89 years from 12 countries with baseline diastolic blood pressures of 90

mmHg to 99 mmHg and/or systolic blood pressures of 160 mmHg to 179 mmHg. Baseline MMSE scores must be within normal range, Dr. Lithell added. Any previous antihypertensive treatment will be standardized to 12.5 mg daily of hydrochlorothiazide among study patients. In addition, an amendment to this trial recommends that doctors give active treatment to all patients if blood pressure exceeds 160/90 mmHg at any time during the study. This is an ethical precaution to ensure the safety of all patients, Dr. Lithell explained.

"AT<sub>1</sub> receptor blockers are a new class of agents and, therefore, studies with hard endpoints are needed for these drugs. SCOPE will provide such information," he said.

### Renal Effects

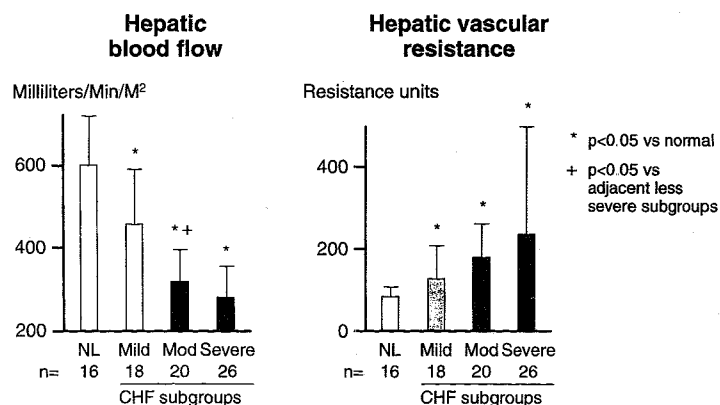
"There is a relatively small percentage of the hypertensive population in which we know exactly which type of drug to use as first-step therapy," according to Dr. Ruilope. There are four situations in which blockade of the angiotensin system is required and forces use of a drug that blocks the effect of angiotensin II. These are hypertension associated with diabetes, chronic renal failure, heart failure, or myocardial infarction. In all of these situations, in theory, an angiotensin receptor antagonist can be considered.

"In the remaining 80% of the hypertensive population, we choose a drug based on efficacy, tolerability, and ease of use in combination therapy," he continued. "Since many patients present with tolerability problems with conventional antihypertensive agents, the newer angiotensin II antagonists may be considered for them as well."

With progressive systolic dysfunction, there is progressive decrease in cardiac index accompanied by a clear increase in peripheral resistances due to decreasing cardiac output effects, Dr. Ruilope explained. "As might be expected, with an increasing degree of heart failure, there is a progressive decrease in the quantity of blood reaching

the kidneys and a progressive increase in renovascular resistances (Figure)."<sup>3</sup>

**Figure.** Hepatic Blood Flow and Hepatic Vascular Resistance (measurements in normal subjects (NL) and subgroups of patients with congestive heart failure (CHF))



### The Angiotensin II Role

In heart failure, angiotensin II over-expresses the physiological actions that normally take place in the kidney. For example, angiotensin II increases aldosterone secretion which, in turn, facilitates sodium retention. Angiotensin II also constricts efferent arterioles and loosens glomeruli exits, which facilitates increasing filtration fraction. The resulting decrease in interglomerular pressure causes more plasma to be filtered, which adds to sodium retention.

"But there are two other possible ways in which angiotensin II facilitates sodium retention," Dr. Ruilope said. "One is through a direct tubular effect which facilitates sodium reabsorption in the proximal tubule. Also, angiotensin II decreases renal medullary blood flow. All of these mechanisms add to sodium retention and what we can expect,

among other things, is an increase in urinary sodium excretion."

In one animal model, treatment with an AT<sub>1</sub> receptor blocker significantly increased natriuresis in the presence of heart failure. Renal plasma flow was no longer decreased in the animals, and renal hemodynamics appeared to be maintained.<sup>4</sup> "The capacity of the kidney to excrete sodium became greater and so the capacity of a drug like this will greatly help us when treating heart failure patients with hypertension. We will facilitate sodium excretion and impede symptoms due to sodium retention," noted Dr. Ruilope.

### Clinical Implications

The decrease in filtration fraction seen when an AT<sub>1</sub> receptor blocker is administered is the only clinical evidence indicating that the intraglomerular pressure is being decreased. When this measure was used in a study of hypertensive type II diabetic patients being treated with one of the drugs, there was a decrease in microalbuminuria accompanying the decreased filtration fraction.<sup>5</sup>

"Microalbuminuria is becoming more and more relevant for several reasons. It is an excellent predictor of cardiovascular risk in normotensive, hypertensive, and diabetic populations. By lowering urinary excretion of albumen with diuretics, we are preventing the appearance of overt diabetic neuropathy. This is similarly effective in both Type 1 and Type 2 diabetes," Dr. Ruilope explained.

In another animal model, AT<sub>1</sub> receptor blocking agent administration significantly decreased glomerulosclerosis,

which is the hallmark of chronic renal failure progression.<sup>6</sup> "Ongoing studies are likely to show that the velocity of renal damage progression leading to end-stage renal failure is clearly decreased by these drugs," he said.

"Whenever we treat hypertension, we can do one of two things. We can pay attention only to lowering blood pressure or we can choose a combination of lowering blood pressure and considering effects beyond only the antihypertensive. Some drugs are extremely efficacious for lowering very high blood pressure but have relatively small capacity for achieving additional effects," Dr. Ruilope concluded.

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