Meeting Report

Satellite Symposia of the Fourteenth Scientific Meeting of the American Society of Hypertension, New York, NY, USA, May 19, 1999

Alexander Scriabine

Yale University Medical School, New Haven, CT.

NEW CLINICAL TRIALS OF ANGIOTENSIN BLOCKADE IN CARDIOVASCULAR DISEASE

The symposium “New Clinical Trials of Angiotensin Blockade in Cardiovascular Disease” was held on May 19, 1999 at the Marriott Marquis Hotel in New York, NY. It was sponsored by Novartis Pharmaceuticals and chaired by Stevo Julius, Professor of Medicine and Physiology, University of Michigan Medical Center, Ann Arbor, MI and consisted of five 25-minute long lectures.

Stevo Julius pointed out that the new family of antihypertensive drugs, angiotensin receptor blockers (ARBs), are remarkably free of side effects and represent a major step forward in the treatment of hypertension. Activation of the renin-angiotensin system contributes to vascular and cardiac hypertrophy and other pathology associated with hypertension. ARBs not only lower arterial pressure but also prevent this pathology. The specific effects of ARBs on cardiovascular pathology must be recognized. The ongoing VALUE trial involving over 14,000 patients in 31 countries is designed to compare valsartan and amlodipine in the treatment of high-risk patients with hypertension and their ability to protect vital organs.

Helmy M. Siragy (University of VA, Charlottesville, VA) discussed the role of AT2 receptors in cardiovascular disease; AT2 receptors share only ca 30% homology with AT1 receptors. Angiotensin II has similar affinity for both receptor types. AT2 receptors mediate the effects of angiotensin II on cell differentiation and development. Their activation has an effect often opposite to that produced by activation of AT1 receptors, e.g. inhibition of growth and dephosphorylation. Stimulation of AT2 receptors increases cGMP, NO, and bradykinin release. AT2 knockout mice have higher sensitivity to the pressor effects of angiotensin II. The expression of AT2 receptors decreases with age but increases

Address correspondence to: Dr. A. Scriabine, Department of Pharmacology, Yale University Medical School, 333 Cedar Street, New Haven, CT 06510 USA.
in response to injury or sodium depletion. Although the functions of AT$_2$ receptors are not yet well established, it appears that they contribute to blood pressure regulation.

The title of Kenneth A. Jamerson's presentation was “Treating Hypertensive High-Risk Patients.” He emphasized the importance of recognizing the cumulative and additive effects of risk factors. Risk factors often cluster and tend to enhance each other. Hypertension is often associated with insulin resistance, decreased plasma HDL, increased plasma triglycerides, obesity, etc. Hypertensive diabetics are more likely to develop renal disease than normotensive diabetics or nondiabetic hypertensives. ARBs tend to slow the progression or to prevent renal disease; they reduce proteinuria. Long-term preventive effects of ARBs, and valsartan, in particular, are currently being evaluated. They are expected to reduce the mortality from cardiovascular diseases.

Marc A. Pfeffer (Harvard University, Boston, MA) spoke about therapeutic options in high-risk patients after myocardial infarction. He advocated the use of both angiotensin converting enzyme inhibitors (ACEIs) and β-adrenoceptor antagonists in patients recovering from myocardial infarction (MI). Statins may also be indicated. All risk factors in post-MI patients should be treated. Hypertension, diabetes, advanced age, and prior MI can all greatly augment the risk of mortality. Clinical trials are now underway to compare the ACEI, captopril, and the ARA, valsartan, in post-MI patient (VALIANT trial). This study is likely to determine whether ARAs have clinically significant advantages over ARAs in post-MI patients with decreased ejection fraction.

Jay N. Cohn (University of Minnesota, Minneapolis, MN) discussed new approaches to the therapy of heart failure. The benefits of ACEIs include reduction of mortality and reduced need for hospitalization. They have beneficial hemodynamic effects, reduce cardiac remodeling, and improve hormonal balance but have only a borderline effect on exercise tolerance and quality of life. The mechanism of their beneficial action may, in addition to the blockade of angiotensin II formation, also include enhancement of bradykinin effects. Some β-adrenoceptor antagonists (carvedilol, bisoprolol, and metoprolol) were also shown to be effective in the therapy of heart failure. Blockade of AT$_1$ receptors may offer additional benefits to heart failure patients.Valsartan was recently shown to produce further improvement in patients receiving lisinopril. ACEIs will prevent the rise of angiotensin II levels in patients receiving valsartan; this effect is likely to be beneficial. A combined therapy with ACEIs and ARAs appears to offer hemodynamic and hormonal benefits in patients with heart failure. A clinical trial of combined therapy of valsartan and an ACEI (Val-HeFt trial) in heart failure patients was recently initiated.

I$_1$ IMIDAZOLINE RECEPTORS: CLINICAL RELEVANCE IN HYPERTENSIVE PATIENTS

The symposium “I$_1$ Imidazoline Receptors: Clinical Relevance in Hypertensive Patients” was held at the Marriott Marquis Hotel in New York on May 19, 1999. It was supported by a grant from Servier Research Group. The symposium was cochaired by Pascal Bousquet (Universite Louis Pasteur, Strasbourg, France) and Guiseppe Mancia (University of Milan, Italy). It consisted of seven 15-minute long presentations.

P. Bousquet discussed the history of discovery of imidazoline receptors. Clonidine binds to specific binding sites in the brain, called imidazoline receptors. The hypotensive
effect of clonidine is mediated by imidazoline receptors, while the sedative effect of clonidine is mediated by $\alpha_2$-adrenoceptors. It is theoretically possible to separate these two effects and to develop clonidine-like antihypertensive drugs with little or no sedative activity. The second generation imidazoline receptor ligand, rilmenidine, is selective for imidazoline receptors, but it does not interact with $\alpha_2$-adrenoceptors. In comparison with clonidine, it produces less sedation. More recently two different subtypes of imidazoline receptors were discovered: $I_1$ and $I_2$. The blood pressure lowering effects of clonidine and rilmenidine are mediated by $I_1$ imidazoline receptor subtype. Imidazoline ($I_1$) and $\alpha_2$-adrenoceptors are involved in the central control of arterial pressure.

Geoffrey A. Head (Baker Medical Research Institute, Prahran, Victoria, Australia) spoke about the role of $I_1$ imidazoline receptors in cardiovascular regulation and the role of rilmenidine. While clonidine and methyldopa act at $I_1$ as well as $\alpha_2$-adrenoceptors, rilmenidine acts preferentially at $I_1$ receptors. Rilmenidine was found to facilitate cardiac vagal baroreflexes and to inhibit cardiac sympathetic baroreflexes. The major site of rilmenidine action is the rostral ventrolateral medulla. $\alpha_2$-Adrenoceptors in the brain stem are also involved and may contribute to rilmenidine-induced blood pressure lowering.

The title of M. Esler’s (Baker Medical Research Institute, Melbourne, Australia) presentation was “The Sympathetic System and Hypertension.” According to Esler, cardiac sympathetic stimulation promotes left ventricular hypertrophy and cardiac arrhythmias. It can also promote the establishment of sustained hypertension. In normotensive obese patients renal norepinephrine spillover is increased, but cardiac sympathetic stimulation is suppressed. In obese hypertensives this suppression may be absent. The blockade of centrally induced sympathetic stimulation by rilmenidine may not only control arterial pressure but also offer cardiac protection.

The clinical overview of the experience with rilmenidine was presented by John L. Reid (University of Glasgow, Scotland, UK). One of the advantages of rilmenidine is that it reduces sympathetic activity without interfering with the physiological responses to changes in posture or exercise. Rilmenidine is well tolerated, even by the elderly. Comparative clinical studies with other antihypertensive drugs revealed that monotherapy with rilmenidine compares favorably with monotherapy with hydrochlorothiazide, captopril, amlodipine, clonidine, or methyldopa. Sudden cessation of therapy with rilmenidine does not lead to withdrawal syndrome. In elderly, diabetic, and dyslipidemic patients rilmenidine improved lipid profile. At 1 or 2 mg once or twice daily, rilmenidine has few, if any, side effects; it produces much less drowsiness than clonidine. In chronic studies rilmenidine decreased ventricular mass and improved left ventricular function. It has a natriuretic effect, apparently at the tubular level. In type II diabetics rilmenidine reduced microalbuminuria. When doses were increased to 8 mg, clonidine-like side effects were observed.

Stevo Julius (University of Michigan, Ann Arbor, MI, USA) spoke about the role of sympathetic overactivity in the pathophysiology of cardiovascular diseases. He emphasized its dangers in hypertension. Sympathetic overactivity is a strong risk factor that can lead to insulin resistance, decreases in HDL levels, increases in hematocrit, thrombosis, or cardiac arrhythmias. Sympathetic stimulation tends to increase the incidence of coronary events; the increase in heart rate tends to increase the incidence of sudden death. Current antihypertensive therapy is not sufficiently effective in the prevention of coronary events.

Olivier Dupuy (Hopital d’Instruction des Armées Begin, Saint Mandé, France) discussed the efficacy of rilmenidine in hypertensive diabetics. Rilmenidine was compared
to captopril in type 2 diabetics in a 6-month study. There was no statistically significant
difference in outcome; both drugs were equally effective in the control of arterial pressure.
Both drugs reduced microalbuminuria. Neither diabetic control nor lipid levels were
affected by either drug.

**Bruno Trimarco** (University of Naples, Italy) compared the effects of rilmenidine (1
mg once or twice daily) and amlodipine (5 or 10 mg once daily) in the management of 43
obese hypertensive patients with hypertriglyceridemia and impaired glucose tolerance in
a 5-month, double-blind study. Both drugs had equal antihypertensive effect and no
effects on plasma lipids. Rilmenidine, but not amlodipine, significantly improved glucose
metabolism.

**IMPACT OF HYPERTENSION AND OTHER RISK FACTORS ON
CORONARY ARTERY DISEASE AND HEART FAILURE**

The symposium “Impact of Hypertension and Other Risk Factors on Coronary Heart
Disease and Heart Failure” was held on May 19, 1999 at the Marriott Marquis Hotel in
New York City. It was supported by Pfizer Inc. and cochaired by **Murray Epstein**
(University of Miami, FL, USA) and **Alan B. Miller** (University of Florida, Jacksonville,
FL, USA). The symposium consisted of seven short lectures.

The first presentation was made by **R. Preston Mason** (MCP-Hahnemann University
School of Medicine, Pittsburgh, PA, USA). The title of his presentation was “Cellular
Mechanisms in Hypertension, Coronary Artery Disease, and Heart Failure.” His labora-
tory studies cellular changes associated with cardiac failure and atherosclerosis. He re-
ported that antioxidants and amlodipine block apoptosis induced by free radicals or
cytokines, and he attributed the beneficial effects of amlodipine in coronary heart disease
and heart failure to its ability to inhibit proliferation of vascular smooth muscle and block
apoptosis.

Amlodipine appears to be more effective than other related calcium antagonists because
it is more lipophylic, enters the cell membrane gradually, and its effects are more per-
sistent.

**Alan B. Miller** (University of Florida, Jacksonville, FL, USA) spoke about the role of
ventricular remodeling in hypertension, ischemic heart disease, and heart failure. Hyper-
tension and coronary heart disease (CHD) are major causes of heart failure. There are 5
million patients with heart failure (HF) in the USA and 20 million worldwide. In HF the
left ventricle is subjected to remodeling, that consists of changes in size, shape, and
function of the left ventricle. With the progression of congestive heart failure, the size of
the left ventricle increases and the pump function is reduced. Angiotensin II and norepi-
nephrine induce the release of other hormones and growth factors that further affect
cardiac function and stimulate remodeling. Reversal of remodeling is one of the therapeu-
tic goals in the treatment of heart failure. Angiotensin converting enzyme inhibitors
(ACEIs) prevent remodeling, and β-adrenoceptor antagonists can also reverse remodeling.

**Christopher M. O’Connor** (Duke University, Durham, NC, USA) discussed the man-
gagement of elderly patients with CHD. The mortality of elderly patients with CHD is
higher than that of younger patients. O’Connor attributed this higher mortality rate to the
fact that aggressive therapy is often not used in the elderly. The risk of renal insufficiency
is also higher in elderly patients with CHD. Among risk factors, hypertension and de-
pression are more common among the elderly; their treatment is important. In selecting a therapy, interactions should be considered. Aspirin may reduce the benefits of ACEIs. Nitrates do not improve survival. Statins should be used more extensively whenever indicated; they are likely to prevent ischemic heart disease in some patients.

Atherosclerosis regression trials were reviewed by Robert P. Byington (Wake Forest University, Winston-Salem, NC, USA). During the last 10 years it became possible to study the effects of various drugs and lifestyle changes on the progression and even regression of atherosclerosis. Angiography, B-mode ultrasonography, and intravascular ultrasound technology made such studies feasible. Each technique has its advantages and disadvantages. Angiography measures the consequence of the disease, not the disease itself; it may miss early stages of the disease. B-mode ultrasonography is noninvasive and requires a smaller sample size; it is now used for coronary arteries. The HERS trial evaluated the effects of estrogens on the progress of CHDs. No significant effect was demonstrated. The PREVENT trial involved the use of amiodipine for the prevention of coronary atherosclerosis. These studies indicated that amiodipine can reduce the number of anginal attacks and revascularization procedures, but no prevention of atherosclerosis was demonstrated.

Murray Epstein (University of Miami, FL, USA) discussed recent trials of calcium antagonists in patients with hypertension and diabetes. Two recent trials: Fosinopril and Amlodipine Cardiovascular Events Randomized Trial (FACET) and Appropriate Blood Pressure Control in Diabetes (ABCD) trial raised concern about the use of calcium antagonists in patients with diabetes. A recent workshop of international experts carefully examined the results and recommended caution in the interpretation of these studies. Considering the potential benefits of blood pressure reduction and beneficial renal effects, calcium antagonists should not be contraindicated in the treatment of hypertensive patients with diabetes.

Peter Carson (Georgetown University, Washington, DC, USA) spoke about the effects of vasodilators on vascular remodeling in hypertension and heart failure. He emphasized the importance of the peripheral vascular effects of drugs in the treatment of heart failure. While ACEIs reduce morbidity and mortality, vasodilator drugs improve ejection fraction and functional capacity acutely. Beneficial effects were reported with a combination of hydralazine and isosorbide dinitrate. ACEIs as well as amiodipine are likely to increase the release of NO. An increase in the availability of bradykinin after ACEIs may have a beneficial effect in the therapy of heart failure. He advocated the polytherapy of heart failure patients with peripheral vasodilators, antiproliferative drugs, and ACEIs.

Milton Packer (Columbia University, New York, NY, USA) outlined current and future management directions for the treatment of hypertensive heart failure. He recommended an aggressive approach and use of all four types of drugs: diuretics, ACEIs, β-adrenoceptor antagonists, and digitalis. If the heart failure patient is normotensive, only a modest fall in arterial pressure can be expected with this regimen.