Meeting Report

Fourteenth Scientific Meeting of the American Society of Hypertension New York City, May 20–22, 1999

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The Fourteenth Annual Meeting of the American Society of Hypertension was held at the Marriott Marquis Hotel in New York City from May 20 through May 22, 1999. The meeting consisted of 163 oral and 653 poster presentations. It was attended by ca. 3,000 participants, mostly physicians from all over the world. This report covers some of the lectures attended by the author and selected posters dealing primarily with the drug therapy.

LECTURES AND ORAL PRESENTATIONS

Giuseppe Bianchi (University of Milan, Milan, Italy) delivered the Richard Bright Award Lecture entitled “Genetics and Pharmacogenomics of Renal Mechanisms of Hypertension.” Bianchi discovered that polymorphism of an α-adducin gene contributes to hypertension in Milan Hypertensive (MHS) rats. Hypertension is caused by increased sodium reabsorption due to stimulation of the renal Na+/K+ pump. In MHS rats, the mutated α-adducin gene causes hypertension by upregulating Na+/K+-ATPase. Similar mutations occur in humans. In collaboration with P. Ferrari (Prassis Sigma Tau, Milan), Bianchi demonstrated that a novel derivative of digitoxigenin, PST 2238, inhibits the Na+/K+ pump and blocks the development of hypertension in MHS rats.

The ASH Special Lecture was delivered by Victor J. Dzau (Harvard University, Boston, MA). It was entitled “New Opportunities in Cardiovascular Medicine: The Role of Genomics.” Dzau visualizes the future application of genome science to the diagnosis, prognosis, and the therapy of many diseases. Different gene mutations affect hormonal and biochemical processes that can in turn, affect the pharmacokinetics and metabolism of drugs and, therefore, influence the response to drugs. The advances in genomic research are likely to lead to greater individualization and safety of therapy. Genomics will also improve clinical trials by allowing a more appropriate selection of patients.

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According to Nancy J. Brown and Douglas E. Vaughan (Vanderbilt University, Nashville, TN), activation of the renin-angiotensin-aldosterone system (RAAS) has a deleterious effect on fibrinolytic balance. Angiotensin II stimulates the expression of the plasminogen activator inhibitor (PAI-1). The levels of PAI-1 are increased in patients with high or even normal renin levels. PAI-1 elevation is a risk factor for myocardial infarction. Angiotensin-converting enzyme inhibitors (ACEIs) lower PAI-1 levels. Low-salt intake or diuretics are likely to activate the RAAS and increase PAI-1 levels.

John H. Laragh (Cornell University, New York, NY) pointed out that prevention of cardiovascular endothelial injury is the primary goal of antihypertensive therapy. Among various available antihypertensive drugs, only beta-blockers and ACEIs reduce coronary and renal vascular events. According to Laragh, beta-blockers achieve these effects by blocking renin release; ACEIs achieve it by blocking formation of angiotensin II. The incidence of heart attacks in patients with hypertension is directly proportional to their plasma renin levels.

W. Linz et al. (Hoechst Marion Roussel, Frankfurt/Main, Germany) reported that long-term blockade of AT1 receptors with fonsartan increases the lifespan of hypertensive rats. The lifespan of stroke-prone spontaneously hypertensive rats (SHR-SP) was doubled by fonsartan (10 mg/kg/d for 15 months). The drug prevented left ventricular hypertrophy and improved cardiac function.

R. San Diego et al. (UCLA, Los Angeles, CA) studied morbidity risk in hypertensive patients (519 blacks and 199 Hispanics) and concluded that use of diuretics is associated with the increased risk of heart disease and that the risk of morbidity is increased with elevated uric acid levels. L. V. Franse et al. (University of Tennessee, Memphis, TN) analyzed data on 4,327 patients and concluded that the use of diuretics was associated with an increase in serum uric acid. The increase in serum uric acid was, however, not associated with an increase in the risk for cardiovascular events.

J. Gasowski et al. (University of Leuven, Belgium) calculated risk rates for cardiovascular events with elevated pulse pressure in elderly hypertensive patients in Europe and China (total of 7,394 patients) and concluded that in elderly hypertensive patients pulse, and not mean pressure, determines cardiovascular risk.

J. C. Burnett et al. (Mayo Clinic, Rochester, MN, and Bristol-Myers Squibb, Princeton, NJ) evaluated omapatrilat, a vasopeptidase inhibitor that inhibits angiotensin-converting enzyme as well as neutral endopeptidase. In SH as well as in DOCA hyper-
tensive rats, omapatrilat dependent manner. It was slightly more potent in DOCA rats. The authors expect omapatrilat to lower arterial pressure in patients independently of their renin status.

N. R. Ferreri et al. (New York Medical College, Valhalla, NY) spoke about regulation and function of cyclooxygenase-2 (COX-2) in the thick ascending limb of rats. Normally only 2% of cells in the thick ascending limb (TAL) are COX-2 positive but, after adrenalectomy, 25% of cells express COX-2. Dexamethasone inhibits COX-2 expression in these cells.

According to H. D. Intengan and E. L. Schiffrin (Clinical Research Institute of Montreal, Quebec, Canada), vasopressin is involved in vascular pathology and blood pressure control in DOCA-salt hypertensive rats. Unilaterally nephrectomized, vasopressin-deficient (Brattleboro) rats on DOCA-salt had lower systolic blood pressure than did Long-Evans rats on the same regimen. The lumen of their mesenteric resistance arteries is also wider.

SELECTED POSTERS

A. Riveiro et al. (Hospital Xeral de Galicia, Santiago de Compostela, Spain) found that in SH rats irbesatran (50 mg/kg/d) or enalapril (20 mg/kg/d) for 24 wks enhanced the vasodilator effects of acetylcholine (as determined in isolated rat aortic rings). The authors concluded that prolonged treatment with these drugs ameliorates endothelial dysfunction.

G. Desideri et al. (University “La Sapienza,” Rome, Italy) compared the effects of four ACEIs (zofenoprilat, lisinopril, enalaprilat, and captopril) on endothelin-1 and NO formation in cultured human endothelial cells (HUVECs). Zofenoprilat was more potent in inhibiting endothelin-1 formation and enhancing NO secretion than were the other ACEIs.

Z. Ni et al. (University of CA at Irvine, CA) reported that, in rats with chronic renal failure, the expression of nitric oxide synthase (eNOS and iNOS) is reduced, while in spontaneously hypertensive (SH) rats the expression of the same enzymes is increased. Felodipine (5 mg/kg/d for 4 wk), administered by osmotic pump, increased the expression of eNOS and iNOS in rats with chronic renal failure, increased it in SH rats, and had no effect on the enzyme expression in normotensive rats.

C. Ferri et al. (University “La Sapienza,” Rome, Italy) found that in hypertensive patients simvastatin reduces blood levels of the vascular adhesion molecule (VCAM-1) as well as LDL levels, while bezafibrate reduces LDL but not VCAM-1 levels. The authors concluded that simvastatin may prevent early arterial activation independent of its effects on cholesterol.

L. Ghiadoni et al. (University of Pisa, Italy) described the effects of candesartan, an angiotensin II receptor antagonist, on endothelial function in the peripheral circulation of essential hypertensive patients. Candesartan was administered orally at 8 mg/d for 2 mo. Forearm blood flow was recorded. At the end of the treatment period, the vasodilator response to acetylcholine (Ach) was increased, and the vasoconstrictor response to endothelin-1 was decreased. Candesartan appears to increase production of nitric oxide.

Q. Diep et al. (Clinical Research Institute, Montreal, Quebec, Canada) found that AT₂ receptors activate the c-Jun amino-terminal kinase (JNK)/stress-activated protein kinase
(SAPK) pathway in PC12W cells that express AT₂ receptors. The authors concluded that angiotensin II induces apoptosis through AT₂ receptors.

J. Sobrino et al. (Hospital de l’Esperit Sant, Santa Coloma de Gramenet, Spain) studied ion transport abnormalities in erythrocytes of hypertensive patients and found that 33% of patients with essential hypertension have abnormal Ca²⁺-dependent ATPase. Serum creatinine and uric acid levels were also elevated in the same patients.

K. Kisters et al. (University Poliklinik, Münster, Germany) studied Ca²⁺ and Mg²⁺ levels in the lymphocytes of hypertensive and normotensive patients and found that intracellular Mg²⁺ levels were significantly lower in hypertensive patients.

R. Garcia-Robles et al. (Alcala de Henares University, Madrid, Spain) studied the effects of irbesatran (50 mg/kg/day for 8 or 12 weeks) on blood pressure and on renal and ocular pathology in male Zucker rats. Irbesatran lowered arterial pressure and had a nephroprotective effect, but it had no effect on retinal alterations.

R. B. Kurashvili et al. (Georgian Diabetes Center, Tbilisi, GA) compared the antihypertensive effects of lacidipine and lisinopril in 69 hypertensive non-insulin-dependent diabetics. The authors concluded that both drugs were equally effective in reducing arterial pressure and albumin excretion in these patients.

A. Mugellini et al. (University of Pavia, Italy) compared the effects of celiprolol, irbesatran, and lisinopril on arterial pressure and insulin sensitivity in 26 nondiabetic hypertensive patients. All three drugs equally reduced blood pressure, but only celiprolol and lisinopril improved insulin sensitivity.

L. H. Roht et al. (Hoechst Marion Roussel, University of Texas, and Medical College of PA) reevaluated the available literature on calcium channel antagonists and cancer using six established epidemiological criteria and concluded that the data do not support a causal relationship between the use of calcium channel antagonists and the development of cancer.

A. Zoppi et al. (University of Pavia, Italy) studied the effects of fosinopril and amlodipine, alone and in combination, on microalbuminuria in hypertensive patients with type II diabetes. The drugs were administered for 3 y. Both drugs were effective in lowering arterial pressure and reducing microalbuminuria. Fosinopril was more effective in reducing microalbuminuria than was amlodipine. The combination of the two drugs was, however, more effective than either drug alone.

W.-P. Huang et al. (Taipei Medical College, Taipei, Taiwan, R.O.C.) found that 6-protoberberine lowered arterial pressure in spontaneously hypertensive rats. This effect
was associated with a reduction in cardiac output and a decrease in heart rate. The authors assume that the drug has a central sympatholytic effect.

**J.-C. Liu et al.** (Taipei Medical College, Taipei, Taiwan, R.O.C.) evaluated the blood pressure-lowering effects of stevioside, a glycoside from *Stevia rebaudiana*. This glycoside is being used in Japan as a sweetener. The study was double-blind and placebo-controlled. After 3 mo of daily administration of stevioside (250 mg, 3 times daily), blood pressure (systolic and diastolic) was significantly reduced in patients receiving the drug. There were no reported adverse effects.

**V. B. Chumburidze et al.** (Georgian Diabetes Center, Tbilisi, GA) evaluated the antihypertensive effects of monotherapy with lacidipine in 50 male patients with hypertension and concomitant heart disease. The drug was administered at 4 to 6 mg, once a day for 6 mo. Lacidipine effectively lowered arterial pressure and produced complete regression of left ventricular hypertrophy in 88% of the patients. An antiischemic effect was also evident: the drug prolonged exercise time and reduced S-T segment depression in the ECG.

**R. Fogari et al.** (University of Pavia, Italy) compared four dihydropyridines (amlodipine, felodipine, lacidipine, and manidipine) for their effects on plasma norepinephrine levels in hypertensive patients. The drugs were administered daily for 12 weeks. Norepinephrine levels were increased in patients receiving amlodipine or felodipine, but not in patients receiving lacidipine and manidipine. It appears that the last two drugs do not activate the sympathetic nervous system.

**F. H. Messerli et al.** (Ochsner Clinic, New Orleans, LA, and Western PA Hospital, Pittsburgh, PA) compared the incidence of vasodilatory edema in patients receiving amlodipine, felodipine, or a combination of these calcium channel antagonists with ACEIs (benazepril or enalapril). There was no difference in the incidence of edema with either

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![Stevioside](image-url)

Stevioside
of the two calcium channel antagonists alone. If an ACEI was added, the incidence of edema was reduced to that of a placebo.

A. H. Gradman et al. (Western PA Hospital, Pittsburgh, PA, and ASTRA Pharmaceuticals, Wayne, PA) compared the antihypertensive efficacy of candesartan cilexetil (16 to 32 mg once daily) with that of losartan (50 to 100 mg once daily) in a double-blind trial on 332 adult patients. Either drug was well tolerated, but candesartan cilexetil was significantly more effective than was losartan in lowering arterial pressure.

According to K. Malmqvist (Karolinska Institut, Stockholm, Sweden), candesartan cilexetil lowers arterial pressure more effectively and is better tolerated than either enalapril or hydrochlorothiazide. He compared the effects of the three drugs in 429 middle-aged hypertensive women treated with one of the three drugs for 12 wk. Candesartan cilexetil lowered systolic blood pressure significantly more than did either of the two other drugs. It produced less cough than enalapril and less hypokalemia or hyperuricemia than did hydrochlorothiazide.

J. Neytel et al. (Orange County Research Center, Orange, CA; University of Texas at San Antonio, TX; Baylor University, Houston, TX; and Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ) compared the antihypertensive efficacy of omapatrilat (5, 10, 20, or 40 mg once a day) with that of lisinopril (20 mg once a day). At 20 or 40 mg, omapatrilat was more effective than was lisinopril at 20 mg. The effect of omapatrilat was independent from either race or age. Omapatrilat is being currently evaluated at doses up to 80 mg once a day in the treatment of hypertension and heart failure.

J. Rossat et al. (Division of Hypertension, CHUV, Lausanne, Switzerland) compared in 12 normal subjects the angiotensin II receptor blockade induced by tasosartan with that induced by its active metabolite, enoltsasartan. The maximal blockade by tasosartan was reached at 1 to 2 h after either i.v. or oral administration and declined to about one half of the maximal at 5 h. The onset of enoltsasartan (i.v.)-induced angiotensin II blockade was slower, and it reached maximal value at 3 to 4 hours and remained at nearly the same level for longer than 32 h. It was concluded that enoltsartan is not likely to contribute substantially to the early phase of tasosartan-induced angiotensin II blockade.

M. Maillard et al., from the same group of investigators, studied the binding properties of tasosartan and enoltsasartan to AT1 receptors. The binding of tasosartan was increased by plasma protein, while that of enoltsasartan was reduced. Warfarin and diazepam
moderately increased the binding of tasosartan to AT_1 receptors, while the binding of enoltasosartan was markedly increased by the same drugs. C. Calvo et al. (University of Santiago, Spain) reported that irbesatran and atorvastatin improve endothelial function in hypertensive and hypercholesteremic men. Either of the two drugs, or both together, reduced the urinary albumin excretion rate and the von Willebrand factor concentration in serum. M. Velasco et al. (University of Venezuela, Caracas, Venezuela, and University Lisandro Alvarado, Barquisimeto, Venezuela) compared the antihypertensive activity of slow-release formulation of nifedipine (nifedipine GITS) and lacidipine in 248 patients. At the end of the 12-wk study, both drugs substantially reduced systolic and diastolic blood pressures. The effect of nifedipine-GITS on systolic pressure was slightly more pronounced than that of lacidipine. Both drugs have a similar effect on natriuresis. L. Alcocer et al., from the same clinic, compared the same two drugs for their effects on the cognitive function of hypertensive patients and concluded that, after 16 wk of treatment, either of the two drugs increases cognition. A. Giusti et al. (Menarini Ricerche, Florence, Italy; The Surgery, Buckinghamshire, U.K.; and Harrison Clinical Research, Munich, Germany) compared the efficacy and safety of zofenopril and amlodipine in 303 patients with mild-to-moderate hypertension.
Zofenopril was administered at 30 mg and amlodipine at 5 mg, both once a day for 12 wk. At the administered doses, both drugs were therapeutically equivalent; they produced comparable reduction in arterial pressure. More patients developed cough with zofenopril than with amlodipine. Amlodipine produced edema in 11% of patients; none of the patients receiving zofenopril developed edema.

M. A. Fortuno et al. (University of Navarra, Pamplona, Spain) found that torasemide, a loop diuretic, also blocks angiotensin II-induced contractions of aortic rings from SH rats with an IC$_{50}$ = 0.04 nmol/L. The angiotensin receptor antagonism may play a role in the mechanism of the antihypertensive effect of torasemide.

C. Ferri et al. (University “La Sapienza,” Rome, Italy) reported that lacidipine reduces circulating levels of the vascular cell adhesion molecule (VCAM-1) in patients with essential hypertension. Atorvastatin has similar effects in patients not receiving lacidipine. In patients on lacidipine, atorvastatin has no further effect on VCAM-1 levels. The authors suggest that lacidipine inhibits LDL peroxidation.

P. Lijnen et al. (University of Leuven, Belgium) studied the effects of three Ca$^{2+}$ channel antagonists [nifedipine, mibefradil, and nordihydroguaiaretic acid (NDGA)], at 0.1 to 1.0 μM, on proliferation of rat cardiac fibroblasts (measured by incorporation of $[^3]$H thymidine) in vitro. All three drugs reduced thymidine incorporation, but NDGA was more effective. NDGA was reported to antagonize T-channels selectively.

A. Mugellini et al. (University of Pavia, Italy) compared the effects of lisinopril vs. losartan on left ventricular hypertrophy (LVH) in 48 hypertensive patients with type II diabetes. Lisinopril reduced LVH to a greater extent than did losartan, while their antihypertensive effects were comparable.

F. C. Barone et al. (SmithKline Beecham Pharmaceuticals, King of Prussia, PA) evaluated the effects of eprosartan on myocardial function and survival of stroke-prone spontaneously hypertensive rats (SHR-SP). Eprosartan was administered at 60 mg/kg/d for 18 wk. All control rats died by 9 wk, while all eprosartan-treated rats were alive at 18 wk. Eprosartan preserved cardiac and renal function and reduced cardiomyopathy and protein excretion in the urine.

F. Muders et al. (University of Regensburg, Germany) administered eprosartan (30 and 60 mg/kg for 4 wk) to rats and found that this angiotensin II antagonist, or its active metabolite, crosses the blood-brain barrier and binds to AT$_1$ receptors in discrete brain areas.

T. N. Thrasher et al. (University of Maryland, Baltimore, MD) studied the effects of irbesartan (50 mg/kg/d in drinking water) on the development of left ventricular hyper-
trophy in rats with experimental aortic stenosis. Irbesartan prevented pressure-induced ventricular hypertrophy.

S. J. Zhu et al. (Third Military Medical University, Chongqing, China) found that benazepril (8 mg/kg/d for 1 mo) inhibits myocardial apoptosis in rats with myocardial infarction induced by coronary ligation. Benazepril is thought to delay the development of heart failure by preventing apoptosis.

M. Garcia-Duran et al. (Jimenez Diaz Foundation, Madrid, Spain) reported that acetylsalicylic acid (1 mg/kg/d for 4 d) normalized the endothelium-dependent vasorelaxant response to acetylcholine in SH rats.