Best of the ASH 2007 Scientific Sessions

Highlights From the 22nd Annual American Society of Hypertension Scientific Meeting and Exposition, May 19-22, 2007, Chicago, IL

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The theme of this year's meeting of the American Society of Hypertension was "Translating Hypertension Research for Cardiovascular Health." Here we describe findings from some of the key presentations. New guidelines from the American Heart Association (AHA) on the treatment of hypertension in the prevention and management of ischemic heart disease were described. In addition, studies provided new data on proteinuria; diabetes; hypertension treatments, including trials of single drug and combination approaches; and insulin resistance and ambulatory blood pressure values in obese adolescents.

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AHA Guidelines

Clive Rosendorff, MD, PhD, presented a scientific statement from the AHA Council for High Blood Pressure Research and the Councils for Clinical Cardiology and Epidemiology and Prevention.[1] The blood pressure goal for primary prevention of heart disease is a level less than 140/90 mm Hg. The goal should be lowered to less than 130/80 for patients with diabetes, chronic renal disease, and coronary artery disease or its equivalent per a Framingham Risk Score consistent with a greater than 10%, 10-year coronary event risk. For patients with heart failure of ischemic etiology, the goal is less than 130/80 mm Hg, but clinicians are urged to aim for a level less than 120/80 mg Hg.

The guidelines also focus on positive lifestyle modifications, including weight loss when necessary, healthy diet, exercise, smoking cessation, and alcohol moderation, which are recommended for all patients. Specific drug indications vary according to the patient group (Table 1). The overall objective of therapy is to reduce excess morbidity and unnecessary deaths.

Proteinuria

George L. Bakris, MD, from the University of Chicago, presented findings from the Comparative Long-Term Effects of Two ARBs on Proteinuria in Patients with Type-2 Diabetes and Overt Nephropathy and Hypertension (AMADEO) trial.[2] The trial tested treatment with telmisartan or losartan in patients with hypertension, type 2 diabetes, or overt nephropathy.

The 860 study subjects had type 2 diabetes mellitus and morning spot urinary protein:creatinine ratio greater than 700 mg/g creatinine. Their levels of serum creatinine were, for women, less than 265 μmol/L (< 3.0 mg/dL) and, for men, less

Table 1
American Heart Association Guidelines for Blood Pressure

Area of Concern	Blood Pressure Target (mm Hg)	Lifestyle† Modification	Specific Drug Indications
General CAD prevention	< 140/90	Yes	Any effective antihypertensive drug or combination‡
High CAD risk*	< 130/80	Yes	ACE inhibitor or ARB *or* CCB *or* thiazide *or* combination
Stable angina	< 130/80	Yes	Beta-blocker *and* ACE inhibitor or ARB
UA/NSTEMI	< 130/80	Yes	Beta-blocker *and* ACE inhibitor or ARB§
STEMI	< 130/80	Yes	Beta-blocker *and* ACE inhibitor or ARB§
LVD	< 120/80	Yes	ACE inhibitor or ARB *and* beta-blocker *and* aldosterone antagonist *and* thiazide or loop diuretic *and* hydralazine/nitrate (in black patients)

*Diabetes, CKD, or CAD or equivalent.
†Weight loss if appropriate, healthy diet, exercise, smoking cessation, and alcohol moderation.
‡Evidence supports ACE inhibitor or ARB, CCB, or thiazide as first-line therapy.
§If the patient has anterior MI, persistent HTN, LVD, heart failure, or diabetes.
CAD, coronary artery disease; UA, unstable angina; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LVD, left ventricular dysfunction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.
Adapted with permission from Rosendorff C et al.[16]

than 283 μmol/L (< 3.2 mg/dL). They had systolic blood pressure greater than 130 mm Hg, diastolic blood pressure greater than 80 mm Hg, or were receiving antihypertensive therapy. The subjects were randomized to receive telmisartan (forced titrated to 80 mg) (n = 419) or losartan (forced titrated to 100 mg) (n = 441).

After 1 year of treatment, the morning spot urinary protein:creatinine was reduced by 29% in the telmisartan group and 20% in the losartan group (P = .0284). Both treatment groups experienced similar reductions in blood pressure. These data suggest that telmisartan may offer greater protection against progression to end-stage renal disease, although this hypothesis requires further study. According to the researchers, the differing effects of angiotensin receptor blockers may be attributable to pharmacological factors such as lipophilicity, magnitude of receptor binding, and duration of action.

Diabetes

Hypertensive patients who have the metabolic syndrome are at higher risk for developing diabetes. Hydrochlorothiazide (HCTZ) increases levels of fasting plasma glucose. Diuretic-induced hypokalemia can inhibit insulin secretion by the pancreatic beta cells, an effect that can be reversed by potassium replacement. Valsartan has been shown to improve insulin sensitivity and to reduce the incidence of new-onset diabetes.[3] A recent study tested treatment with HCTZ and valsartan, alone and combined. Results from the Metabolic Assessment of Valsartan vs Thiazide Therapy in Pre-Diabetic Patients with Metabolic Syndrome (MADE-ITT) trial were presented by James R. Sowers, MD, of the University of Missouri, Columbia.[4]

Five hundred and sixty-six prediabetic, hypertensive patients with abdominal obesity were studied. The treatment arms were valsartan 320 mg (n = 189), HCTZ 25 mg (n = 190), and valsartan 320 mg/HCTZ 25 mg (n = 187). After 16 weeks of therapy, there was no significant change in a homeostasis model assessment of insulin resistance among the 3 groups. The fraction of patients who achieved blood pressure control was significantly higher in the combination valsartan/HCTZ group as compared with the single-agent groups (Figure 1). Hemoglobin A_{1c} levels were significantly increased with HCTZ versus valsartan. HCTZ, by itself, had the greatest effect on increasing levels of high sensitivity C-reactive protein in prediabetic patients with the metabolic syndrome. Valsartan, as solo therapy, had the least effect on increasing these levels.

Aliskiren Versus HCTZ

Roland E. Schmieder, MD, of the University of Erlangen in Germany, presented findings from the study Aliskiren-Based Therapy Lowers Blood Pressure More Effectively Than

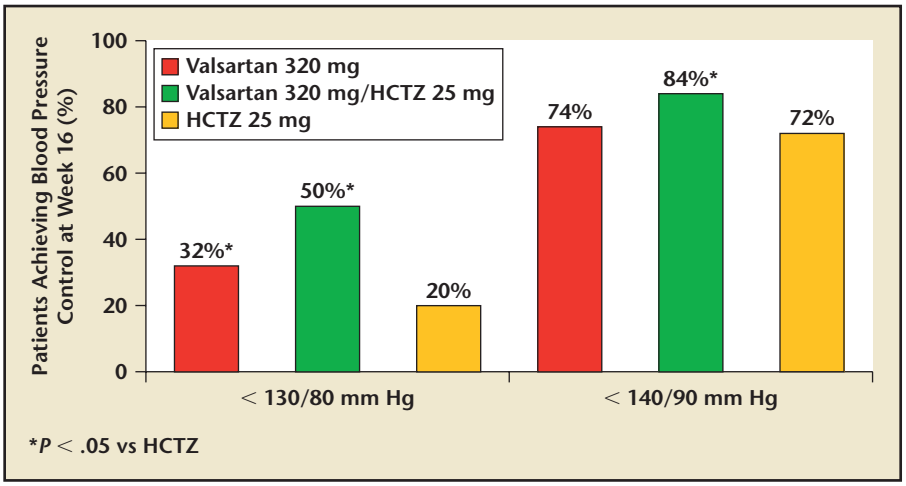


Figure 1. *The fraction of patients who achieved blood pressure control was significantly higher in the combination valsartan/HCTZ group as compared with the single-agent groups. HCTZ, hydrochlorothiazide. Adapted with permission from Sowers JR.*[4]

HCTZ-Based Therapy.[5] *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) recommends that thiazide-type diuretics be used as first-line agents for the treatment of hypertension.[6] Thiazides block sodium reabsorption and stimulate renin release, which causes an increase in plasma renin concentration and plasma renin activity. Aliskiren, the first direct renin inhibitor approved for the treatment of hypertension, has been shown to lower plasma renin activity. This trial is the first to compare the long-term antihypertensive efficacy of aliskiren-based therapy with HCTZ-based therapy.

The study group consisted of 124 patients with mild to moderate hypertension (mean sitting diastolic blood pressure ≥ 95 and < 110 mm Hg). They received either aliskiren 300 mg monotherapy or HCTZ 25 mg monotherapy. (After 12 weeks, patients in both groups also received amlodipine as needed for blood pressure control.) The percentage of patients who achieved blood pressure control was higher in the aliskiren groups than in the HCTZ groups (Figure 2). Aliskiren-based therapy also provided greater suppression of the renin system over 12 months in patients who had hypertension.

Combination Therapy

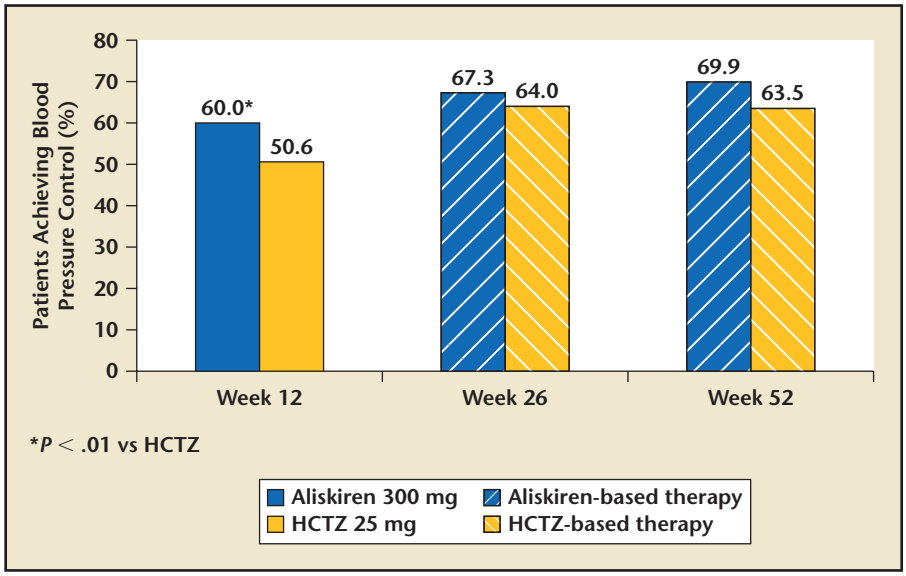
Guidelines from the JNC 7,[6] the International Society on Hypertension in Blacks,[7] and the European Society of Hypertension[8] all recommend that combinations of 2 drugs be initiated in patients in whom single agents are unlikely to achieve blood pressure targets. Combination therapy can target complementary mechanisms of action and thereby achieve superior blood pressure reduction.

Benazepril/HCTZ Versus Amlodipine/Benazepril

Preliminary results from the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial were presented by Kenneth A. Jamerson, MD, of the University of Michigan in Ann Arbor.[9]

The ACCOMPLISH trial is the first clinical outcomes trial in hypertension to compare 2 established forms of fixed-dose combination therapy. The treatment arms were benazepril/HCTZ (forced titrated to 40/12.5 mg) and amlodipine/benazepril (forced titrated to 5/40 mg). The 11,400 subjects were older than 55, and they either had a systolic blood pressure above 160 mm Hg or were currently

Figure 2. *The percentage of patients who achieved blood pressure control was higher in the aliskiren groups than in the HCTZ groups. HCTZ, hydrochlorothiazide. Adapted with permission from Schmieder RE.*[5]



taking antihypertensive therapy and had evidence of either cardiovascular disease, renal disease, or other target organ damage.

After 18 months, the rates of blood pressure control were higher than those of any other multinational trial. Overall control rates (< 140/90 mm Hg) increased from 37% to 76%. The mean systolic blood pressure decreased from 145 to 131 mm Hg. The researchers stated that these results "provide substantial evidence to broaden the use of combination therapy as an initial strategy for the treatment of hypertension."

Amlodipine and Valsartan in Patients After Monotherapy

Joseph L. Izzo, MD, of the State University of New York at Buffalo, presented results of a Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy of the Combination of Amlodipine and Valsartan in Hypertensive Patients Uncontrolled on Previous Monotherapy.[10] Previous data have shown that fixed-dose combination of the angiotensin receptor blocker valsartan and the dihydropyridine calcium antagonist amlodipine has achieved greater reductions in blood pressure than either agent alone.[11]

The 894 subjects had systolic blood pressure of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg (or ≥ 130/80 mm Hg for the diabetic subpopulation). Their high blood pressure had not been adequately controlled with monotherapy. Patients received combination amlodipine/valsartan. Two doses of amlodipine were tested: 5 mg and 10 mg. The dose of valsartan was 160 mg. HCTZ add-on therapy was permitted after week 8 if necessary to control blood pressure.

By week 16, change from baseline systolic blood pressure was −18.0 mm Hg for the 5/160 mg dose and −20.8 mm Hg for the 10/160 mg dose (intention-to-treat analysis; $P < .001$). The proportion of patients achieving BP of less than 140/90 mm Hg is shown in Figure 3. The switch from a single agent to valsartan-amlodipine conferred a 20 mm Hg decrease beyond the reductions seen with previous medications. Up to 75% of subjects achieved the recommended target goals. In the diabetic patient subgroup, more than 40% achieved the recommended target of less than 130/80 mm Hg.

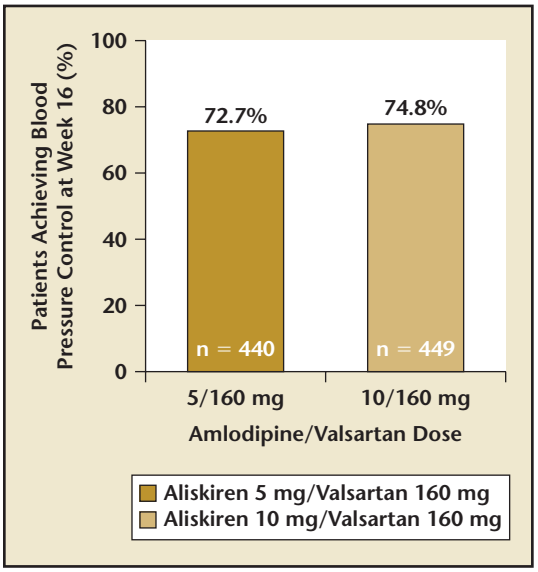


Figure 3. The proportion of patients achieving blood pressure of less than 140/90 mm Hg is shown. Adapted with permission from Izzo JL.[10]

Amlodipine/Valsartan Combination Therapy Versus Monotherapy

The amlodipine/valsartan combination was also studied in the trial Dual Calcium Channel & Angiotensin II Receptor Blockade is Superior to Amlodipine or Valsartan Alone for Optimal Hypertension Control. Results were presented by Thomas Philipp, MD, of the University of Duisburg-Essen in Essen, Germany.[12] This trial aimed to determine if amlodipine/valsartan combination therapy provided superior blood pressure reductions and control compared with single agents in patients with mild to moderate hypertension.

The study group consisted of 1250 patients with diastolic blood pressure between 95 and 110 mm Hg. Combination therapy with amlodipine and valsartan provided better hypertension control compared with either agent alone (Figure 4). Median systolic blood pressure was reduced to less than 140 mm Hg by the second week with combination valsartan/amlodipine. The number of patients in whom blood pressure levels dropped to less than 140/90 mm Hg increased incrementally throughout the study in the amlodipine/valsartan combination group.

Amlodipine and Olmesartan Versus Monotherapy

Steven G. Chrysant, MD, of the University of Oklahoma in Oklahoma City, presented results from A Randomized, Double-Blind, Placebo-Controlled Factorial-Design Study Evaluating the Efficacy and Safety of Coadministration of Amlodipine and Olmesartan vs Monotherapy.[13]

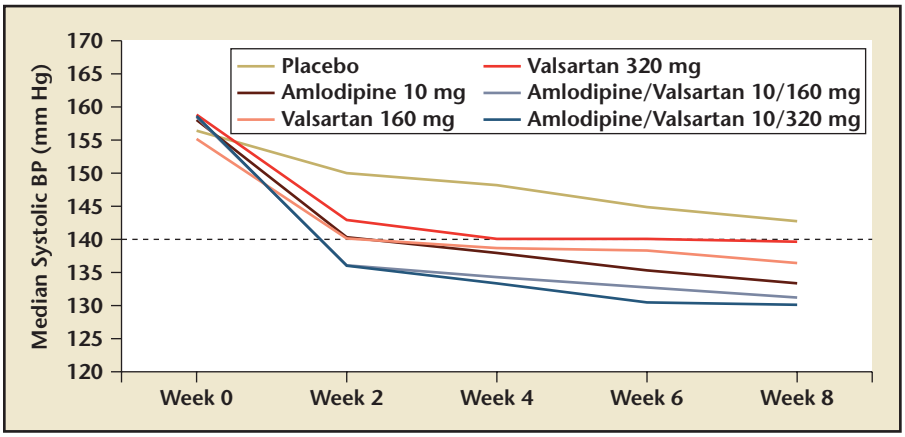


Figure 4. *Combination therapy with amlodipine and valsartan provided better hypertension control compared with either agent alone. BP, blood pressure. Adapted with permission from Philipp T.*[12]

This study tested amlodipine and olmesartan in combination and as monotherapy.

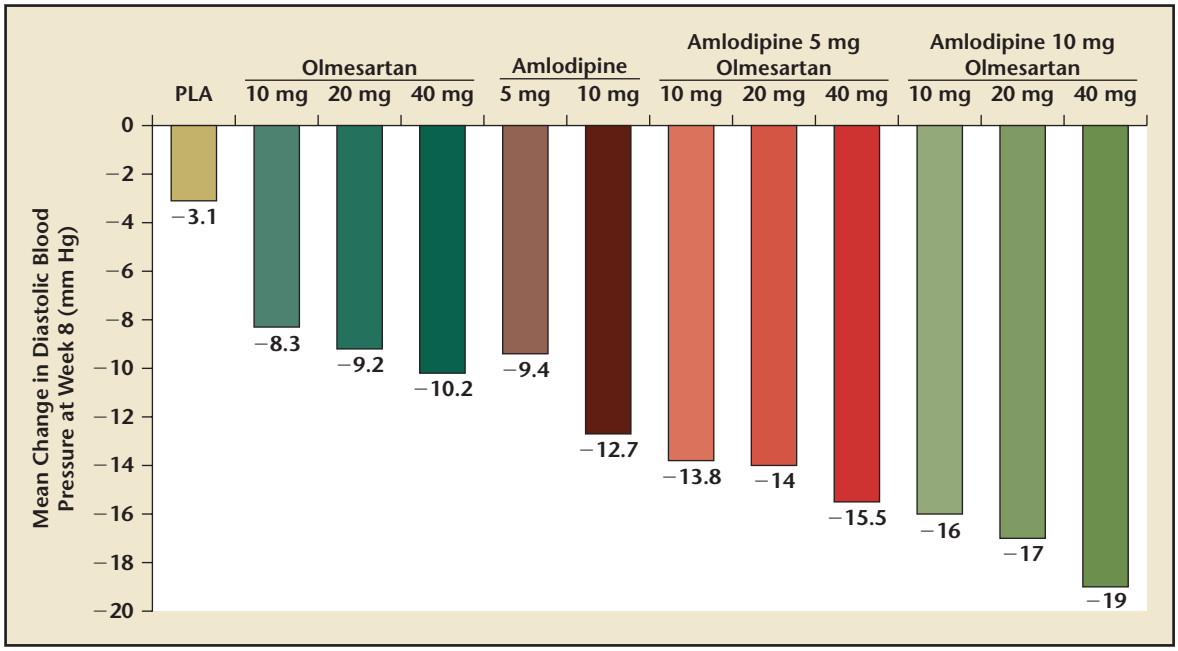
The study group was 1940 patients with mild to severe hypertension (mean sitting diastolic blood pressure between 95 and 120 mm Hg). The treatment arms consisted of amlodipine combined with olmesartan at various dosages and each of the agents separately at different dosages. The combinations of amlodipine and olmesartan achieved greater systolic blood pressure reductions as compared with the individual monotherapies (Figure 5). Blood pressure reductions were dose related in the patients treated with the amlodipine-olmesartan combinations.

Addition of Once-Daily Nebivolol to Ongoing Antihypertensive Therapy

Alan H. Gradman, MD, of the Western Pennsylvania Hospital in Pittsburgh, presented data from a study on the Addition of the Beta Blocker Nebivolol to Ongoing Therapy in the Management of Mild to Moderate Hypertension.[14] Beta blockers are well established in the management of hypertension and cardiovascular disease. Nebivolol is a novel, highly cardioselective, beta-1 adrenergic receptor blocker that is combined with nitric oxide–mediated vasodilating action.

The 669 patients had mild to moderate hypertension (sitting diastolic blood pressure levels between 90 mm Hg and 109 mm Hg) and were already receiving a stable regimen of antihypertensive therapy. The treatment arms were nebivolol at 5 mg, 10 mg, and 20 mg. The addition of nebivolol significantly reduced blood pressure in a dose-dependent

Figure 5. *The combinations of amlodipine and olmesartan achieved greater systolic blood pressure reductions as compared with the individual monotherapies. Adapted with permission from Chrysant SG.*[13]



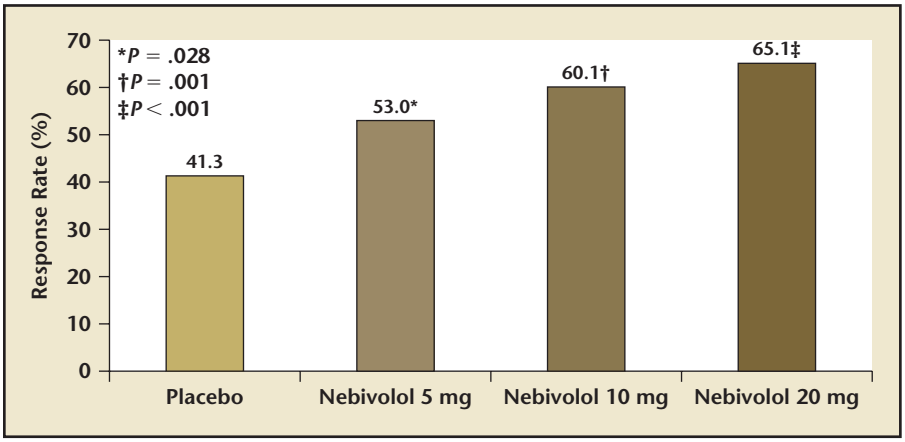


Figure 6. *The addition of nebivolol significantly reduced blood pressure in a dose-dependent manner. The response rate was the reduction in mean trough sitting diastolic blood pressure to less than 90 mm Hg or a decrease from baseline of at least 10 mm Hg. Adapted with permission from Gradman AH.*[14]

manner (Figure 6). It was also well tolerated.

[Norman E. Lepor, MD, FACC, FAHA, FSCAI]

Insulin Resistance and Hypertension in Children

Patients with high blood pressure, as a group, are more likely to be insulin resistant, glucose intolerant, hyperinsulinemic, and dyslipidemic than patients without high blood pressure. There is substantial evidence suggesting that insulin resistance and/or compensatory hyperinsulinemia have a role in blood pressure regulation and may predispose a patient to develop high blood pressure. Overall, the current evidence indicates that insulin resistance and compensatory hyperinsulinemia occur in approximately 50% of adults with hypertension, and the presence of these abnormalities in normotensive individuals predicts the eventual development of essential hypertension. What, however, had not been studied to date was the relationship between insulin resistance and hypertension in children. With the increasing prevalence of overweight and obesity in children, this relationship has become a matter of significant public health concern.

A study presented by Empar Lurbe, MD, of the Hospital Clinico at the University of Valencia in Spain, analyzed the relationship between insulin resistance and ambulatory blood pressure values in obese adolescents.[15] The study group consisted of 87 overweight and obese white children and adolescents (both male and female). Obesity was defined on the basis of a threshold body mass index z score of greater than 2 (Cole's lambda-mu-sigma [LMS] method). Overweight was defined as a body mass index in the 85th to 97th percentile. Fasting glucose and insulin values were measured to determine placement in the homeostatic model

There is substantial evidence suggesting that insulin resistance and/or compensatory hyperinsulinemia have a role in blood pressure regulation and may predispose a patient to develop high blood pressure.

Main Points

- For patients with heart failure of ischemic etiology, the blood pressure goal is less than 130/80 mm Hg, but clinicians are urged to aim for a level less than 120/80 mg Hg.
- Telmisartan may offer greater protection than losartan against progression to end-stage renal disease.
- In a study of prediabetic, hypertensive patients with abdominal obesity, the fraction of patients who achieved blood pressure control was significantly higher in the combination valsartan/hydrochlorothiazide group as compared with single-agent groups.
- More patients with mild to moderate hypertension achieved blood pressure control while taking aliskiren than hydrochlorothiazide.
- Preliminary results from the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial suggest that combination therapy could be used more broadly as an initial strategy for the treatment of hypertension.
- In overweight and obese children and adolescents, insulin resistance was associated with higher nocturnal blood pressure and heart rate levels.

assessment (HOMA) index. Subjects were then grouped into tertiles of the HOMA index. Ambulatory blood pressures were measured in all subjects over a 24-hour period.

No significant differences were seen in age, sex, and body mass index z-score distribution among the groups. When adjusted for age, sex, and height, nocturnal systolic blood pressure and heart rate were significantly increased in subjects in the highest HOMA index tertile (HOMA index $>$ 4.7; average 6.8) as compared with those of the other groups. No differences were observed for daytime systolic blood pressure or daytime heart rate.

In overweight and obese children and adolescents, insulin resistance was associated with higher nocturnal blood pressure and heart rate levels. The early increment of nocturnal blood pressure and heart rate associated with hyperinsulinemia may be a harbinger of hypertension-related insulin resistance and may contribute to the cardiovascular risk associated with this condition.

Obesity has become an increasingly important medical problem in children and adolescents. In national surveys from the 1960s to the 1990s, the prevalence of overweight in children grew from 5% to 11%. Hypertension is an important adverse outcome related to childhood obesity. The current study suggests that in obese children, just as in obese adults, insulin resistance may predate development of hypertension, which may first manifest nocturnally. ■

[Karol E. Watson, MD, PhD]

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