recommended as first-line agents in patients with type 1 diabetes or renal disease, patients who have had an MI, and patients with heart failure.

Key Words: Hypertension, Combination Therapy, ACE Inhibitors, Diuretics

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ACCOMPLISH—the First Clinical Trial in Mortality Reduction with Antihypertensive Combination Therapy

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The use of combination therapy is a superior strategy for controlling blood pressure when compared to monotherapy. The possibility that specific combination therapies could improve cardiovascular outcomes has not been previously studied.

Angiotensin II may play an important role in promoting coronary atherosclerosis because of its effect on endothelial function and subsequent vasconstriction, abnormal smooth cell migration, macrophage activation, and promotion of platelet aggregation.

There is also a potential role for calcium channel blockers (CCBs) in the atherosclerotic process. A review of scientific research provides support for several anti-atherosclerotic mechanisms for amlodipine: antioxidant activity and increased resistance of lipids to oxidative stress, remodeling of vascular smooth muscle cell membranes, inhibition of smooth muscle cell proliferation and migration, and enhancement of endothelial nitric oxide (NO) production.

An additive increase in NO production is a possible pathway of synergy for angiotensin-converting enzyme (ACE)/CCB combination drug therapy. A recent study has evaluated the effects of an ACE-inhibitor, amlodipine, and their combination on vasodilation and NO production in canine coronary microvessels. While both agents increased NO production, the combination had a synergistic effect and marked NO formation.

The ACCOMPLISH trial is the first major hypertension outcomes trial that will randomize subjects to a specific fixed-dose combination drug as initial therapy. An exciting possibility is that specific drug combinations may confer target organ protection in addition to and independent of their blood pressure lowering effects. The ACCOMPLISH study will evaluate whether the fixed-dose combination of amlodipine/benazepril (Lotrel) provides added benefits in reducing morbidity and mortality from cardiovascular events in a high-risk hypertensive population when compared with an ACE-inhibitor (benazepril) diuretic combination.

Key Words: clinical trials, combination therapy, event driven trials

HOW SHOULD COMBINATION THERAPY BE STARTED?

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The latest guidelines for the treatment of hypertension recommend stratification of blood pressure (BP) goals according to patient risk level. For example, the recommended BP goal for high-risk patients such as those with diabetes, cardiovascular (CV) disease, or renal insufficiency is <130/85 mm Hg or <130/80 mm Hg—lower than the <140/90 mm Hg target for patients with uncomplicated hypertension. However, epidemiologic data show that only about 27% of hypertensive people in the United States have their BP controlled to <140/90 mm Hg, indicating the need for improved antihypertensive treatment. Major trials show that 40% to 50% of all patients require multiple antihypertensive agents to achieve their BP goal. The failure of monotherapy to control BP in trials of stepped-care drug strategies has led to a renewed and growing interest in combination antihypertensive therapy.

Combination therapy has been shown to address the multiple pathophysiologic factors that play a role in BP elevation, including blood volume, vasocostriction, and the impact of sympathetic nervous system and renin-angiotensin system (RAS) activity, potentially resulting in both greater reduction in BP and in lowered risks for target-organ damage. The use of a fixed, low-dose combination agent also offers lower doses of each component than those that may be necessary with monotherapy, thus reducing the risks of dose-dependent adverse events (AEs) and associated compliance problems. These benefits may be enhanced when an angiotensin-converting enzyme (ACE) inhibitor is used as a component agent. While agents that block the RAS have been amply demonstrated to provide both renal and cardiac protection in hypertensive patients, independent of BP reduction, these effects may be amplified in combination with an agent with a complementary mechanism of action. For example, the ALERT (A Lotrel Evaluation of Hypertensive Patients with Arterial Stiffness and Left Ventricular Hypertrophy) trial compared the effects of amlodipine/benazepril combination therapy with those of monotherapy with the component drugs on arterial distensibility and left ventricular mass (LVM). Combined ACE inhibitor and calcium channel blocker (CCB) treatment was more efficacious than high doses of the individual agents in increasing arterial compliance and reducing LVM.

Use of a combination agent may thus be appropriate as initial therapy in patients at high CV risk, such as those with diabetes, CV disease, renal insufficiency, or any combination of these risk factors. Furthermore, because multiple antihypertensive agents are necessary to achieve BP goals in close to half of all patients, use of combination therapy in addition to, or in replacement of, a failed monotherapy—in a stepwise manner—is also a rational option. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), for example, found that a diuretic-based regimen reduced CV risk to a similar extent as did CCB-based and ACE inhibitor–based regimens. However, after the 5-year treatment period of ALLHAT, 9.0% of subjects given a diuretic initially had switched to CCB or ACE inhibitor monotherapy, and an additional 13.2% were taking a CCB or ACE inhibitor with a diuretic; the average number of antihypertensive agents required by each subject was 1.8. Switching to, or adding, a fixed, low-dose ACE inhibitor/CCB combination therapy rather than monotherapy with either component may be significantly more effective and safer. An open-label study including more than 6000 patients with diastolic BP values between 90 and 110 mm Hg, despite amlodipine monotherapy, found that switching patients to amlodipine/benazepril combination therapy produced an additional mean reduction in BP of 15.6/11.5 mm Hg (P<0.001 vs amlodipine monotherapy). Furthermore, the incidence of pedal edema, a common AE associated with CCB therapy, was improved in 85% of patients experiencing the problem.

Along with diuretics, ACE inhibitors and CCBS are 2 of the most effective and widely used antihypertensive agents available. Emerging evidence suggests the optimal use of these agents may be in fixed, low-dose combination therapy rather than as monotherapies.

Key Words: Amlodipine, Benazepril, Antihypertensive Therapy

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Wednesday, May 14, 4:00 PM–6:00 PM

Hypertension in the Obese Patient: Pathogenic Mechanisms, Cardiovascular Risk, and Treatment*

THE OBESITY EPIDEMIC AND CV RISK

William H Dietz, Centers for Disease Control and Prevention, Atlanta, GA

Obesity is now epidemic in the United States. Children and adolescents appear to be at particularly high risk, and the increases in the prevalence of overweight children and adolescents doubled between NHANES III (1988-1994) and the current NHANES (1999-2000). Although over-
weight children and adolescents account for only 25% of obese adults. Overweight children who become overweight adults tend to be heavier than adults whose obesity began in adulthood. Cardiovascular disease risk factors, such as abnormal glucose tolerance, hyperlipidemia, and blood pressure are increased among overweight children. These data suggest that childhood-onset overweight may contribute a disproportionate share of morbidity and mortality of obesity in adulthood. Furthermore, these trends suggest that the recent declines in cardiovascular disease will likely be reversed if the epidemic of obesity proceeds unabated.

*This activity is supported by an unrestricted educational grant from Pfizer Inc.

INTRODUCTION: HYPERTENSION IN THE OBESE PATIENT: PATHOGENIC MECHANISMS, CARDIOVASCULAR RISK AND TREATMENT
Lewis Landsberg, Northwestern University, Chicago, IL

The worldwide increase in obesity has led to a number of adverse health consequences including hypertension, coronary artery disease, and type 2 diabetes. This symposium will consider obesity and hypertension, focusing on pathogenesis, cardiovascular risk, and management.

Projections indicate that the prevalence of obesity in the United States may approach 50% by 2030. What is the cause of this remarkable increase in obesity? Clearly dietary excess and physical inactivity are critically important. But people differ significantly in their capacity to resist weight gain. Some individuals gain weight incrementally in the face of increased caloric intake while others dissipate the caloric load by increasing their metabolic rate, a phenomenon known as dietary thermogenesis. An efficient metabolism that does not waste ingested calories is one component of what has been called a “thrifty metabolic trait”; the other component involves sensitivity to the action of insulin on glucose uptake. Resistance to this action of insulin fosters utilization of non-glucose substrates by muscle while preserving glucose for use in the brain, a tissue that requires glucose, but not insulin, for normal function. Both components of this “thrifty” trait would prolong survival during periods of famine, and would therefore be favored by evolutionary pressures. In the face of a plentiful food supply, however, the thrifty trait predisposes to obesity and type 2 diabetes. Since most of the untoward consequences of obesity occur in postreproductive life, selective pressures against the thrifty trait would be minimal.

The hypertension of obesity involves insulin and leptin, both of which stimulate the sympathetic nervous system as a compensatory mechanism recruited to stabilize body weight. Body fat distribution also contributes to the complications of obesity. Adipocytes within the abdomen produce angiotensinogen, suggesting that enhanced angiotensin-2 production may contribute to elevated blood pressure.

*This activity is supported by an unrestricted educational grant from Pfizer Inc.

CONCLUDING REMARKS
Lewis Landsberg, Northwestern University, Chicago, IL

The hypertension that occurs in association with obesity confers substantial cardiovascular risk and warrants an aggressive therapeutic approach. This should include lifestyle modifications that foster weight loss and enhance insulin sensitivity as a part of every therapeutic regimen. Although rarely sufficient in and of themselves, these lifestyle changes improve the response to antihypertensive medications and exert a beneficial effect on other aspects of the risk profile associated with obesity and hypertension.

Combinations of antihypertensive drugs should be employed to achieve blood pressure levels in the range of those recommended for patients with type 2 diabetes. Agents that improve the metabolic profile (rather than those associated with deterioration of that profile) should be considered as part of the antihypertensive drug combination.

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TREATING HYPERTENSION IN THE OBESE PATIENT
Suzanne Opal, University of Alabama at Birmingham, Birmingham, AL

Obesity is associated with high blood pressure (BP). The Framingham Heart Study has shown that for every 10% increase in weight, systolic BP increases by 6.5 mm Hg. Treatment begins with accurate measurement of BP using an appropriate sized cuff and determination of the body mass index (BMI) and waist circumference to assess total fat burden and fat distribution. Weight loss therapy that combines dietary changes emphasizing calorie reduction, increased physical activity, and behavior modification to reinforce maintenance of lifestyle changes is the cornerstone of antihypertensive treatment. Loss of as little as 10 pounds has been associated with significant BP reductions. Pharmacologic treatment should include a thiazide-type diuretic, generally in combination with another agent, such as a calcium channel blocker, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker. Combination therapy both enhances BP lowering and alleviates the glucose intolerance and hypokalemia associated with high-dose diuretics. Unless indicated for a comorbid condition, β-blockers should not be used because they may worsen insulin resistance and glucose intolerance.

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Wednesday, May 14, 4:00 PM-6:00 PM
New Therapeutic Strategies to Optimize Blood Pressure Control and End-Organ Protection*

THE IMPORTANCE OF TIGHT BLOOD PRESSURE CONTROL: IS THE CLASS OF ANTIHYPERTENSIVE AGENT CRITICAL?
William C. Cashman, Veterans Affairs Medical Center, Memphis, TN

Hypertension is a major independent risk factor for CV disease. The chief aim of therapy remains that of lowering BP to recommended goals (<140/90 mm Hg for most hypertensive patients). Large clinical trials have been conducted to determine whether antihypertensive drugs differ in their ability to reduce CV events. A meta-analysis by the Blood Pressure Lowering Treatment Trials’ Collaboration reported that angiotensin-converting enzyme (ACE) inhibitors, beta blockers, diuretics, and calcium channel blockers (CCBs) all provided similar reductions in CV morbidity and mortality. However, recent findings of the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study showed that the angiotensin II receptor blocker (ARB) losartan potassium reduced CV events 13% more than did atenolol as initial therapy for hypertensive patients with left ventricular hypertrophy. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), the largest hypertension trial ever conducted, found that the diuretic chlorthalidone was superior to the ACE inhibitor lisinopril, the CCB amlodipine besylate, and the alpha blocker doxazosin in reducing 1 or more major CV events. Other trials have supported the specific benefits of inhibiting the renin-angiotensin system with ARBs or ACE inhibitors for slowing the progression of diabetic and hypertensive renal disease. Thus, drug classes do differ in their ability to reduce CV events and other outcomes, and it is therefore important which drugs are selected at least as initial therapy. Diuretics should be included as initial therapy in most antihypertensive regimens. ARBs have demonstrated efficacy comparable to that of other antihypertensive classes, with a tolerability profile similar to that of placebo. They may therefore be valuable in the management of hypertension, especially in combination.