the concentration and turnover of plasma non-esterified fatty acids. In fact, we found that the reduction in BP of obese hypertensives treated with ACE inhibition correlated with the improvement of insulin’s ability to suppress fatty acids (N=11, r = -0.73, p<0.01). These data raised the possibility that tissue (adipocyte) ACE contributes to obesity hypertension in part through adverse effects on lipid (fatty acid) metabolism. It is tempting to speculate that improvement of insulin’s fatty acid lowering action contributed to the reduction in new onset diabetes in HOPE. Angiotensin synergistically enhances the production of reactive oxygen species in vascular smooth muscle cells (VSMCs) stimulated with oleic acid, an effect no antagonized by Vitamin E. The reactive oxygen species are critical signaling molecules in the migration and proliferation of VSMCs stimulated with oleic acid and angiotensin. The expression of ACE and AT1 receptors is increased in atherosclerotic plaque, especially the shoulder regions, which are vulnerable to rupture and incite thrombosis. Proteins, which destabilize the plaque, are present in the shoulder areas and activated by oxidative stress. The local amplification of angiotensin production (ACE) and action (AT1 receptors) in concert with the lipid abnormalities of the cluster would serve to accelerate vascular remodeling and the associated vascular catastrophes by augmenting oxidative stress, which is probably not attenuated by Vitamin E. The highly beneficial outcomes with drugs that interrupt the RAS in high risk subjects are consistent with the basic science data. Paradoxically, the benefits of ACE inhibition in HOPE may have been mediated by antioxidant actions, whereas Vitamin E was ineffective. Utilization of agents which inhibit the RAS among high risk, insulin-resistant subjects prior to the development of diabetes mellitus and hypertension may prevent these manifestations of the cluster and the vascular complications that ensue.

*This activity is supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals, Inc.

Wednesday, May 16, 10:00 AM to 12:00 PM
New Directions in Hypertension Management - Beyond JNC VI*

AN ANALYSIS OF RECENT CLINICAL TRIALS AND THEIR IMPACT ON JNC VI GUIDELINES

Marvin Moser 1Yale University School of Medicine, New Haven, CT, United States

Hypertension treatment prior to 1996 and 1997 demonstrated a dramatic decrease in both cerebrovascular and cardiovascular events with diuretic and beta blocker therapy. On the basis of this experience, the JNC VI recommended that these agents be used as initial therapy unless there were specific indications for other medications. Since that time several trials have been published comparing older medications, specifically diuretics and beta blockers with newer medications, i.e., ACE inhibitors and calcium channel blockers (CCBs). In addition, trials comparing CCB treated patients with ACE inhibitor treated patients have also been published. Results indicate that the use of a beta blocker/diuretic-based treatment program will reduce morbidity/mortality to the same degree as ACE inhibitor/ CCB-based programs both in diabetics, non diabetics and in the elderly. Studies with CCBs also indicate that these agents may be less effective in reducing myocardial infarction and heart failure than diuretics or ACE inhibitors but may be more effective in reducing strokes. The recommendations of the JNC for the use of diuretics or beta blockers as initial therapy except in special situations is still reasonable. Based on results of the UKPDS, the Japanese, the STOP-2 in the Elderly, and the NORDIL and INSIGHT studies, certain changes may be indicated in these recommendations. Evidence suggests that an ACE inhibitor with or without a diuretic should be added to the list as initial treatment along with diuretics and beta blockers. While CCBs are effective and generally well tolerated, it would appear that the beneficial effects of these agents on CHD events is less than when ACE inhibitors or diuretics are used. The necessity to use multiple medications to reduce blood pressure to goal levels has been confirmed.

Key Words: Hypertension, clinical trials, JNC VI, therapy

*This activity is supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals, Inc.

Wednesday, May 16, 1:00 PM to 3:00 PM
Hypertension in Older Persons*

VASCULAR CHANGES OF AGING

Stanley S. Franklin 1University of California, Irvine, CA, United States

Population studies have shown that systolic blood pressure (SBP) rises linearly from adolescence through old age, whereas diastolic blood pressure (DBP) levels off at age 50 and decreases after age 60. Thus, pulse pressure (PP), the gap between SBP and diastolic blood pressure (DBP) begins to increase from age 50-59 years with acceleration of this increase from age 60 onward. The Framingham Heart Study examined the relationship between BP and coronary heart disease (CHD) risk as a function of age. In the younger age group (<50 years old), DBP was a more powerful predictor of CHD risk than was SBP. Recent studies using radial artery waveform recorded non-invasively by applanation tonometry have shown that peripheral amplification of SBP from the aorta to the brachial artery decreases as peripheral DBP increases in the under age 50s, but not in older subjects. This may explain why peripheral DBP is a better predictor of risk than peripheral SBP in younger subjects. Thus, both small vessel resistance and altered pulse wave reflection are important hemodynamic mechanisms in hypertension of the young. With aging, however, the Framingham studies showed that the best predictor of CHD risk shifted from DBP to SBP and by age 60 to PP. Much evidence suggests that PP is a surrogate marker for large artery stiffness. Thus, CHD risk in the middle-aged and elderly is more related to the pulsatile stress of large artery stiffness during systole than the steady stress of vascular resistance during diastole. Furthermore, the greatest burden of hypertension-related CHD occurs in the middle-aged and elderly, in whom wide PP isolated systolic hypertension predominates.

Key Words: Hypertension, aging, pulse pressure, coronary disease

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

Wednesday, May 16, 1:00 PM to 3:00 PM
Hypertension in Older Persons*

TREATMENT OF HYPERTENSION IN OLDER PATIENTS

Marvin Moser 1Yale University School of Medicine, New Haven, CT, United States

Benefit of treatment in older patients whether they have isolated systolic hypertension (ISH), defined as systolic blood pressure >140 with a diastolic pressure <90 mm Hg, or diastolic/systolic hypertension >140/ >90 mm Hg has been demonstrated. Both cerebrovascular and cardiovascular events have been reduced by treatment. Therapy should include lifestyle changes; most specifically weight reduction if appropriate and sodium restriction. Elderly patients are more sensitive to salt restriction than younger patients. If medications are used, blood pressure response should be monitored with standing blood pressures. Medication should be titrated more slowly and a physician should hold off on adding therapy if symptoms occur as blood pressures are lowered. A decrease of only 20 mm Hg systolic blood pressure may produce excellent results; it is often not possible to reduce systolic blood pressure in older patients to goal levels <140 mm Hg. Therapy has been shown to be beneficial in those under and over 80 years of age. A low-dose diuretic is probably the drug of choice in most patients. If this is not effective at a dose of 12.5 - 25 mg or the equivalent of hydrochlorothiazide, the addition of a low-dose beta blocker, an ACE inhibitor, an ARB, or a CCB is indicated. Based on trial data, alternative therapy in ISH should be a low-dose CCB. If this is not effective, a low-dose diuretic should be added. Combination therapy, i.e., diuretic/ACE-I, diuretic/beta blocker, diuretic/ARB, or diuretic plus a CCB are acceptable as initial therapy in older patients. Addition of or a
change in therapy should be approached cautiously if the diastolic blood pressure decreases <55-60 mm Hg.

Key Words: Hypertension, older persons, therapy

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

Wednesday, May 16, 4:00 PM to 6:00 PM
Sympathetic Nervous System, II Imidazoline Receptors, Hypertension and Metabolic Disorders*

I1 RECEPTORS, CARDIOVASCULAR FUNCTION, AND METABOLISM

P. Bousquet 1Laboratoire de Neurobiologie et Pharmacologie Cardiovasculaire, Université Louis Pasteur, Faculté de Médecine, Strasbourg, France

Injected into the medullary site of the hypotensive action of clonidine, imidazolines and related compounds decrease blood pressure whereas no phenylethylamine compounds were capable of producing such an effect as the same site. There is much biochemical and pharmacological evidence to support the involvement of imidazoline receptors in the regulation of vasomotor tone as well as in the mechanism of action of some centrally acting antihypertensive drugs. Imidazoline specific binding sites (IBS), which do not recognize catecholamines, have been described in various tissues. Functional studies using selective antagonists have confirmed that the hypotensive effects of clonidine-like drugs are mediated, at least in part, by non-adrenergic imidazoline-specific receptors, while there sedative action clearly involves a2-adrenergic receptors located in the locus coeruleus. Compared with clonidine, newer centrally acting antihypertensive drugs such as rilmenidine are more selective for imidazoline receptors than for a2-adrenergic receptors. This selectivity may explain the reduced incidence of side effects of these drugs at therapeutic doses. Very recently, imidazoline-like compounds with no affinity and no activity at a2-adrenergic receptors have become available. Some of these compounds lowered the blood pressure when injected centrally, indicating that an action on imidazoline I1 receptors alone is sufficient to cause hypotension. Nevertheless, imidazoline receptors and a2-adrenoceptors cooperate in the control of the vasomotor tone and in the hypotensive action of centrally acting hybrid drugs (ie, drugs which bind to both types of receptor). Additional non-cardiovascular effects of imidazoline-like drugs have also been described, such as insulin secretion stimulation and renal sodium reabsorption inhibition. These effects may account for long term benefits of imidazoline selective drugs, such as rilmenidine.

Key Words: Imidazoline receptors, a2-adrenergic receptors, rilmenidine

*This activity is supported by an unrestricted educational grant from SERVIER

Wednesday, May 16, 4:00 PM to 6:00 PM
Sympathetic Nervous System, II Imidazoline Receptors, Hypertension and Metabolic Disorders*

DIABETES: THE BENEFITS OF BLOOD PRESSURE AND METABOLIC CONTROL IN HYPERTENSION

S. Julius 1University of Michigan Health System, Ann Arbor, MI, United States

Whereas individual research papers about antihypertensive treatment in diabetics might be somewhat confusing, the weight of the evidence strongly suggests that:

1. In patients with type 1 diabetes, it is advantageous to use angiotensin-converting enzyme (ACE) inhibitors as primary treatment.
2. In type 2 diabetes, aggressive blood pressure (BP) lowering is warranted and, the calcium antagonist controversy notwithstanding, all drugs appear to be similarly useful in reducing cardiovascular mortality. Specifically, in the SystEur study, compared with placebo, a calcium antagonist dramatically reduced cardiovascular (CV) events in elderly diabetics. The HOT study showed that, using a calcium antagonist-based regimen, the degree of BP lowering determines the degree of CV event reduction. Furthermore, the UKPDS did not find a difference in CV events reduction in patients treated with beta-blockers or with ACE inhibitors. In the UKPDS, the effect of BP lowering on reduction in CV events was more substantial than the degree of CV reduction by blood sugar lowering.
3. Both the CAPP and the HOPE study found that treatment with an ACE inhibitor may be useful in reducing the incidence of new-onset type 2 diabetes mellitus.
4. Insulin resistance, a precursor of diabetes mellitus and a strong predictor of future CV disease, is differentially affected by antihypertensive treatment. Beta-blockers and diuretics worsen insulin resistance, whereas alpha-adrenergic blockers and central imidazoline agonists increase insulin sensitivity. The effect of ACE inhibitors and angiotensin blockers may also positively affect insulin resistance but the results are not uniformly positive.

It stands to reason that the differential effect of various drugs on insulin resistance and primary CV may be clinically relevant particularly in the course of the long-term prevention of mild hypertension. All current trials investigate the effect of the treatment on secondary prevention of