Friday, May 17, 6:30 AM - 8:00 AM
Sunrise Seminar Series: Angiotensin II Blockade in the Management of Cardiovascular Disease

ANGIOTENSIN II BLOCKADE IN THE MANAGEMENT OF CARDIOVASCULAR DISEASE

James R. Sowers, SUNY Downstate, Brooklyn, NY, United States.

Angiotensin 2 plays a key role in the pathogenesis of hypertension and CV and renal disease. Randomized controlled trials shown that ACE inhibitors provide cardiovascular and microvascular benefits and may also improve insulin resistance and prevent the development of diabetes. Furthermore, ACE inhibitors provide considerable benefits in diabetic patients with heart failure, and reduced left ventricular mass and left ventricular dilation and significantly reduced mortality and hospitalization for heart failure. Thus, ACE inhibitors are currently recommended as a first line treatment for patients with hypertension and diabetes particularly those with proteinuria as well as those with heart failure. Data from randomized controlled trials in patients with type 2 diabetes suggest that ARBs may be considered equal to ACE inhibitor for renal protection. For example, the Reduction of Endpoints in NIDDM with the Angiotensin Losartan (RENEAL) trial demonstrated that angiotensin II receptor blocker combined with conventional antihypertensive treatment as needed confers significant renal protection in patients with type 2 diabetes and nephropathy. The risk of the primary end point (a composite of doubling of serum creatinine, end stage renal disease or death from any cause) was reduced by 16% with losartan. The risk of doubling of serum creatinine was reduced by 25% and the risk of end stage renal disease was reduced by 28% over a follow up period of 3.4 years. The study also documented reduction in the initial hospitalization for heart failure. These benefits were above and beyond those attributable to BP reduction alone, suggesting that ARBs, like ACE inhibitors, have special beneficial cardiovascular/renal benefits in diabetic patients.

Key Words: Angiotensin Therapy, Diabetes Mellitus

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BEYOND BLOOD PRESSURE EFFECTS OF ALL BLOCKADE

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Research on the development of atherosclerotic plaque and the mechanisms of acute coronary syndromes has identified multiple levels of input from the Renin Angiotension System. Drugs that block the Type I receptor for ANG II have joined ACE inhibitors as effective strategies to protect patients with atherosclerotic vascular disease as well as hypertensive and diabetic renal disease.

This vascular protection may be attributable to inhibition of the mitogenic effects of Angiotensin II, thus reducing ventricular and vascular hypertrophy. Yet, many authorities now attribute this benefit to the improvement in endothelial dysfunction. The prime mechanism may be inhibition of NADH and NADPH oxidases, which then curtails production of reactive oxygen species. Thus preventing activation of transcriptional factors such as NF-kB and initiation of the inflammatory cascade, (an obligatory part of the plaque development as well as its eventual destabilization). Recent reports have examined the independent effects of Type I and Type II Angiotensin receptors on inflammatory cytokines and plaque development and confirmed the role of the Type II receptor. Clinical studies have validated the antihypertensive effects of blocking the type I receptor for angiotensin II. By also repressing left ventricular hypertrophy, this therapeutic intervention has impacted a formidable risk factor for stroke and myocardial infarction. The data from ValHeFT is a further indication of the benefit that can be expected from incorporating ANG II receptor blockade in the treatment of patients with left ventricular dysfunction. We have also learned of the benefit of Angiotensin II blockade in hypertensive patients with Type 2 DM and renal insufficiency. Studies presented last year at these meetings documented a renal protective effect that had not been validated in primary outcome studies with ACE inhibitors.

The potential of combining ACEIs’ and ARBs’ in patients at atherosclerotic risk is now under active investigation, along with studies on the interdependence of receptors for ANG II and oxidized LDL. This talk will focus on the newer aspects of Angiotensin II inhibition.

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Saturday, May 18, 6:30 AM - 8:00 AM
Compliance With Antihypertensive Therapy: Is it Time for Chronotherapy?

IS IT TIME FOR CHRONOTHERAPY?

Janice G. Douglas, Case Western Reserve University, University School of Medicine, Cleveland, Ohio, United States.

Blood pressure and heart rate follow a circadian rhythm, peaking between the hours of 6:00 AM and 12:00 noon. The early morning surge in blood pressure has been linked to an increased occurrence of acute myocardial infarction, sudden cardiac death, silent ischemia, and stroke during these critical hours. Specifically, there is a 40% higher risk of heart attack, a 29% increased risk of cardiac death, and a 49% increased risk of stroke during this period. From a clinical standpoint, optimal antihypertensive therapy needs to provide 24-hour blood pressure control. Unfortunately, most of the currently available once-daily therapies do not deliver medications synchronized with the body’s circadian rhythm. Chronotherapeutic drug formulations, for this reason, may provide an added benefit to the treatment of hypertensive patients, as these agents offer 24-hour blood pressure control from a single daily dose and provide improved blood pressure control during the early morning BP surge. Antihypertensive regimens that provide improved control of blood pressure during high-risk periods may reduce adverse outcomes and sequelae, particularly in high-risk patients. It is critical for specialist to evaluate the role of chronotherapy in hypertension management, thereby enabling them to make informed treatment decisions, and advocate to primary care providers, based upon their assessment of the body of evidence in the professional literature. Furthermore, selecting drug treatments that correlate with specific circadian variations in BP may provide alternative treatment options for improving the management of hypertensive patients.

1. Elliot WJ. Cyclic and circadian variations in cardiovascular events. AJH. 2001; 14:291S-295S
2. Glasser SP, Neutel JM, Albert KS, et al. Efficacy and safety of diltiazem HCl extended release (CDR) dosed at nighttime (10PM) compared to placebo and to morning dosing (8AM) in moderate to severe essential hypertension [abstract]. AJH. In press.

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Saturday, May 18, 1:30 - 3:30 PM
Combination Drug Therapy for High Risk Hypertensive Patients

DIABETES MELLITUS: EVIDENCE-BASED RATIONALE FOR COMBINATION THERAPY

Murray Epstein, Dept. Medicine, University of Miami School of Medicine, Miami, FL, United States.

Recent data from the United States Renal Data System (USRDS) indicate that despite attempts to control blood pressure, the incidence of end stage
renal disease (ESRD) secondary to diabetic nephropathy has become the leading cause of ESRD in the United States. Hypertension is acknowledged to be a major risk factor in the progression of diabetic renal disease. Developing an effective therapeutic regimen for the control of hypertension in patients with diabetes is therefore essential to retard ESRD in this population. A recent Consensus Conference of the National Kidney Foundation (NKF) provided compelling evidence that lowering elevated blood pressure slows the decline in GFR. Based on these considerations, both the NKF and the American Diabetes Association (ADA) advocate a BP goal of 130/80 mmHg for diabetic patients. How best to achieve this objective is the focus of investigation. Several recent studies, including the UKPDS and HOT, have demonstrated that multiple drug therapy is required to achieve a lower goal blood pressure in the diabetic hypertensive patient. Results of recent landmark diabetic nephropathy trials, including RENAAL and IDNT, are consistent with this position. In RENAAL, monotherapy with losartan alone did not achieve goal blood pressure. Indeed, the average number of drugs needed to achieve the goal blood pressure exceeded 3. This presentation will review the clinical evidence from these trials that confirms the need for a multiple drug regimen in managing the diabetic hypertensive patient.

RISK IN THE AFRICAN AMERICAN: A MANDATE FOR COMBINATION THERAPY
Kenneth A. Jamerson, University of Michigan Health System, Ann Arbor, MI, United States.

Epidemiologist’s survey’s show that the prevalence of hypertension (HTN) in African Americans exceeds the rates of most race/ethnic groups in the US. This ethnic difference is more remarkable regarding the most severe forms and complications of (HTN). The excess incidence of hypertensive nephropathy (nearly 18-fold greater in younger subjects) taken together with putative differences in renal handling of sodium, reports of expanded plasma volume, and low plasma rennin activity has provided a platform to suggest the African Americans may have unique manifestations of HTN. Recent evidence from the African American Study of Kidney Disease and Hypertension (AASK) suggest otherwise.

The AASK Study recruited nearly 1100 subjects with impaired renal function due to HTN. The diagnosis was confirmed by renal biopsy in a sample of the cohort. The goal of the trial was to assess the effects of aggressive blood pressure (BP) control and three different drug regimens on renal function after four years of follow-up. Each therapy consistent of combinations of antihypertensive drugs that differed in composition by only one agent: metoprolol, ramipril, or amlodipine. In subjects with the greatest degree of renal impairment and at least 300 mg of protein in the urine, ramipril was the therapy best able to preserve renal function. Ironically, nearly 70% of the subjects were on calcium channel blockers at entry into the study. The combination regimens and effective BP control attenuated the decline in renal function to levels slightly in excess of those observed with the normal aging process. The rate of decline in the AASK cohort is similar to the rate observed in predominately Caucasian cohorts. The implication of the AASK result is that combination therapy with the appropriate agents can eliminate race/ethnic differences in renal failure. The soon to be completed Aflah trial disclosed similar findings in its interim analysis of combination therapies. There were trivial differences in cardiovascular (CV) event rates when comparing African American to other race ethnic groups.

Combination therapy diminishes the clinical importance of any of the putative pathophysiological explanations for racial differences in CV event rates. The optimal BP target that will impart maximal CV protection remains elusive. It is, however, clear from prospective trials with large numbers of African Americans that combination therapy is essential to eroding the racial gap in CV disease.

Key Words: hypertension, treatment, combination therapy, African Americans

COMBINATION DRUG THERAPY FOR HIGH-RISK HYPERTENSIVE PATIENTS
Le Michael Prisant, Hypertension Unit, Medical College of Georgia, Augusta, GA, United States.

The primary rationale for combination therapy is to enhance blood pressure control by using drugs that have an additive effect (e.g. diuretics and beta-blockers or calcium antagonists and converting enzyme inhibitors). However, complicated and sometimes costly drug regimens can result in noncompliance and the risk of adverse events increases with the use of high doses of these drug combinations. Fortunately, new fixed-dose combination antihypertensive drugs can improve compliance by simplifying dosing regimens and decreasing dose-dependent side effects, thus improving blood pressure control while reducing cost.

Awareness and treatment of hypertension in the United States has been growing among three high-risk groups: African Americans, patients with type II diabetes mellitus, and those with chronic renal insufficiency. Despite advances in treatment, however, hypertension continues to be poorly controlled in many patients. The blood pressure goal for patients with type II diabetes mellitus is a systolic <130mmHg and diastolic <80mmHg. If gross proteinuria is present, then a tighter range is recommended. However, actual attained control rates are low, despite potent data demonstrating the reduction of cardiovascular events by treating diastolic hypertension and isolated systolic hypertension. New data show a reduction in the progression of renal insufficiency with angiotensin receptor blockers and an actual reduction in total and cardiovascular mortality with angiotensin converting enzyme inhibitors. There are no outcome data to determine which combination of drugs optimizes nephroprotection and cardiac protection, but it is suspected that angiotensin converting enzyme inhibitors with nondihydropyridines may be optimal.

African Americans have a disproportionate number of risk factors, including diabetes mellitus, left ventricular hypertrophy, obesity, and decreased leisure-time physical activity. In addition, congestive heart failure, sudden cardiac death, acute coronary ischemia, stroke, and renal insufficiency are more common in blacks than whites. Thus, target blood pressure for African Americans should be similar to that set for patients with type II diabetes mellitus. In blacks with renal insufficiency, angiotensin converting enzyme inhibitors are superior to beta-blockers or dihydropyridine calcium channel blockers. More outcome data are needed to confirm the optimal combination of drugs that are vascular-protective.

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