In selecting a drug from a particular class such as ACE inhibitors, it seems prudent to limit the selection to those that have solid documentation of substantial clinical efficacy and long-term safety. It is equally important to prescribe the full recommended dose. An untested drug should be considered an unproven drug.

Key Words: Class effect; ACE inhibitors; clinical trials

Thursday, May 18, Marquis Ballroom, 6:30 AM to 8:00 AM
Understanding the Role of Angiotensin II in Hypertension and Beyond

THE EVIDENCE FOR ACTIONS OF ANGIOTENSIN II ON VASCULAR GROWTH
Ernesto L. Schiffrin. Clinical Research Institute of Montreal, Canada

Angiotensin II (Ang II) exerts its vascular effects on blood pressure through vasoconstriction, its effects on remodeling of blood vessels and via induction of endothelial dysfunction. These effects of Ang II on smooth muscle growth and collagen deposition are mediated mainly by AT\textsubscript{1}, which may be blocked by specific antagonists such as irbesartan, an effective orally active antihypertensive drug. AT\textsubscript{1} receptors act via G proteins and phospholipase C activation, increasing free cytosolic calcium, which results in smooth muscle cell contraction. Via activation of tyrosine kinases, AT\textsubscript{1} receptors stimulate the ras-raf-MAPKK-ERK1/2 pathway among others, leading to cell growth. Growth factors such as bFGF, PDGF, TGF\textbeta, EGF, IGF, etc., are stimulated, generation of superoxide anions occurs, and endothelin production by endothelial cells is increased. Blockade of AT\textsubscript{1} receptors may avoid the deleterious effects resulting from AT\textsubscript{1} receptor activation. By leaving AT\textsubscript{2} receptors unblocked, AT\textsubscript{2} receptor antagonists may allow Ang II to stimulate AT\textsubscript{2} receptors, which may be beneficial, contributing to regression of vascular remodeling. Interruption of the renin-angiotensin system with angiotensin converting enzyme inhibitors in humans and in experimental animals corrects vascular structure and endothelial dysfunction, whereas beta-blockade does not. In spontaneously hypertensive rats administration of the AT\textsubscript{1} receptor antagonist irbesartan corrected small artery remodeling and mechanics, including collagen deposition and adhesion molecule changes, and endothelial dysfunction. We therefore investigated the effects of an AT\textsubscript{1} receptor antagonist, losartan, in comparison to the \beta-blocker atenolol, on abnormalities of gluteal subcutaneous resistance arteries in 19 patients with essential hypertension in a double-blind randomized trial. Both treatments reduced blood pressure comparably. After one year of treatment, the media width to lumen diameter ratio of arteries from losartan-treated patients was significantly reduced whereas that of arteries from atenolol-treated patients was unchanged. Endothelium-dependent relaxation was normalized by losartan but not by atenolol. In conclusion, Ang II exerts growth effects on small arteries of humans via AT\textsubscript{1} angiotensin receptor activation, and AT\textsubscript{1} antagonism corrects the altered structure and endothelial dysfunction of resistance arteries from essential hypertensive patients. The growth-inhibitory action of AT\textsubscript{1} receptor antagonists results in a vascular protective effect that could contribute to reduce complications of hypertension, which remains to be demonstrated.

Key Words: Resistance arteries; remodeling; hypertrophy; hyperplasia; endothelial dysfunction

THE RENIN SYSTEM AND CARDIOVASCULAR DISEASE: LESSONS FROM PHARMACOLOGICAL INTERVENTION
Colin I. Johnston. Baker Medical Research Institute, Melbourne

The renin angiotensin system (RAS) plays an important pathophysiological role in hypertension and its consequences including cardiac and renal failure. In hypertension it elevates blood pressure and regulates body fluid homeostasis. It is also involved in left ventricular hypertrophy and target organ damage. However there is now increasing evidence that the RAS is also involved in atherosclerosis and pathological consequences. Angiotensin infusion increases vascular superoxide production and impairs endothelial function both of which are corrected by angiotensin receptor (ATR) blockers. Angiotensin’s pleiotropic actions contribute to the inflammatory process in atherosclerosis by activating the expression of chemoattractant and adhesion molecules as well as inducing cytokines and growth factors. It also stimulates smooth muscle transformation, replication, hypertrophy and migration. Angiotensin is formed locally by activated macrophages and fibroblasts which migrate through the plaque and stimulate metallo-proteinases and extracellular matrix deposition and degradation. This leads to an unstable plaque which together with angiotensin’s prothrombogenic activity contributes to thrombosis formation and acute myocardial infarction. Numerous publications have demonstrated that blockade of the RAS by either ACE inhibitors or ATR blockers ameliorates atherosclerosis in dietary, genetic or molecular manipulated hyperlipidaemic rabbits, primes and mice. The HOPE Study extends this role to the clinical situation.

These multiple actions of angiotensin form the rationale for the cardiovascular and renoprotective effects of blocking the RAS and for the clinical benefits of angiotensin receptor blockers.

Key Words: Renin; angiotensin; ACE inhibitors; angiotensin blockade; atherosclerosis

Saturday, May 20, Broadway Ballroom North, 6:30 AM to 8:00 AM
Improvement in Clinical Outcomes in Hypertension: Advantages of Angiotensin Receptor Blockers

ISSUES IN HYPERTENSION: DRUG TOLERABILITY AND SPECIAL POPULATIONS
Haralampos Gavras, M.D. Boston University School of Medicine, Boston, MA

It has been shown that only 25% of hypertensives are well controlled, whereas 27.5% are inadequately treated and 47.5% not treated at all. Reasons for this include poor compliance due to complicated dosing regimens (multiple doses, difficulty to follow instructions), drug-related side effects, inappropriate drug combinations leading to adverse inter-