INTRODUCTION

Ever since the Framingham study established hypertension as a risk factor of coronary artery disease (CAD), the purpose of treating hypertension is to reduce mortality and prolong survival. Worldwide, annually 7.5 million deaths (13% of all deaths) are attributable to high blood pressure (BP); related diseases, particularly cardiovascular diseases (CVDs). For that reason, the guidelines of hypertension and cardiology societies emphasize that hypertension treatment should aim at reducing the long-term risk of cardiovascular morbidity and mortality.\(^2,3\)

BLOOD PRESSURE LEVELS VERSUS CHOICE OF TREATMENT

The benefits of antihypertensive treatment on cardiovascular morbidity are thought to be mainly due to the BP-lowering effects, independent of the class of drug employed, as has been demonstrated with beta-blockers (BBs), diuretics, calcium channel blockers (CCBs) and recently with the renin-angiotensin-aldosterone system (RAAS) inhibitors.\(^2\) But, present clinical evidence in our disposal does not conclusively provide answers to whether it is BP levels or the drug class which is important while selecting a specific treatment strategy. The second Australian National Blood Pressure (ANBP2)\(^4\) study which compared an angiotensin-converting enzyme inhibitor (ACEI) with hydrochlorothiazide concluded that initiation of antihypertensive treatment involving ACEI in older subjects lead to better outcomes than treatment with diuretic agents, despite similar reductions of BP. On the other hand, the hypertension optimal trial (HOT) stated that the lowering of BP per se was associated with a lower risk of cardiovascular events.\(^5\)

OPTIMAL TREATMENT STRATEGIES FOR HYPERTENSION

The definitions relating to hypertension have changed significantly over the years, as have opinions concerning optimal BP targets, especially as they relate to patients with comorbidities. Initial recommendations for therapy to achieve this goal very likely will continue to involve lifestyle modifications as are recommended by various guidelines. If these fail or are inadequate, then pharmacologic therapy will be necessary.

Review of literature suggests that despite the known benefits of various drug classes, there has been no clear consensus on the choice of the drug therapy. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)\(^6\) study published in the Journal of the American Medical Association (JAMA) in the year 2002 for the first time compared three drug classes for the choice of initial treatment which included a thiazide type diuretic (chlorthalidone), ACEI (lisinopril) and a CCB (amlodipine) the results indicated that thiazide type diuretics should be considered first for pharmacologic therapy in patients with hypertension. For patients who cannot take a diuretic, first-step therapy with CCBs and ACEI could be considered. The ALLHAT was instrumental in shaping the Joint National Committee (JNC) 7 guidelines to endorse the role of thiazide type diuretic as an initial therapy. Beta-blockers which were once a corner stone in the management of hypertension fell out of favor as in comparison with other antihypertensive drugs. The effect of BBs (atenolol) was found to be less than optimal with an increased risk of stroke when compared to losartan in the Losartan Intervention for Endpoint (LIFE) Study.\(^7\) Guidelines suggested that in the absence of established CAD or heart failure BBs should not be used as initial therapy.\(^2\)

Joint National Committee 7 has provided guidelines for selection of initial drug choices in doing so, patients with “compelling indications” are defined.\(^8\) These represent comorbidities such as CAD, diabetes mellitus, heart failure, postmyocardial infarction, chronic kidney disease and recurrent stroke prevention, where particular drug classes have been proven as beneficial based on outcomes studies/evidenced-based conclusions from studies or existing clinical guidelines (Figure 1).

Without compelling indications and for stage 1 hypertension (systolic BP 140–159 mm Hg, diastolic BP 90–99 mm Hg), thiazide-type diuretics are considered as adequate therapy for most individuals. Similarly, for stage 2 hypertension (systolic BP 160 mm Hg, diastolic BP 100 mm Hg) two drugs in combination should be prescribed for most individuals (a thiazide-type diuretic and ACEI), or angiotensin receptor blocker (ARB), or BB, or CCB.

The European Society of Hypertension/European Society of Cardiology (ESH/ESC) hypertension guidelines published back in 2007 stated all classes of antihypertensive drugs should be potentially considered as first choice.\(^1\) However, JNC7 guidelines indicate that ACEIs have more compelling indications as compared with ARBs, indirectly supporting a greater beneficial effect of one drug class as compared with the other.\(^8\) It is worth noting that the only indication specific for ARBs is the cough caused by the ACEIs.

THE STORY OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BLOCKERS

The blood pressure lowering treatment trialists’ collaboration (BPLTC) assessed the blood pressure-dependent and independent effects of ACEIs and ARBs on major cardiovascular events in patients with hypertension, diabetes, a history of coronary heart disease, or cerebrovascular disease in a meta-analysis which included 26
trials involving either drug class. The authors reported similar BP dependent effects of ACEIs and ARBs for the risk of stroke, coronary heart disease and heart failure. In terms of blood pressure-independent effects, however, only ACEIs was associated with a significant additional relative risk reduction for major coronary disease events of 9%.

A 2011 meta-analysis included all randomized clinical trials comparing ARBs with controls (placebo or active treatment), with a total of 37 randomized trials and 147,000 patients. When compared with controls, ARBs were not found to be associated with a reduction in risk of myocardial infarction (MI) [relative risk (RR) 0.99; 95% confidence interval (CI) 0.92–1.07]. There was also no detectable beneficial effect for the outcome of MI in trials comparing ARBs versus placebo (RR 0.93; 95% CI 0.81–1.07), as well as for the outcome of all-cause or cardiovascular death, despite lower BP with ARBs. When compared with active treatment, the relative risk of MI with ARBs was 1.04 (95% CI 0.98–1.11), while all-cause and cardiovascular death were also not reduced. While these meta-analyses point out of significant differences between and ARBs, despite being in clinical use, there has been no head-to-head comparison between ACEIs and ARBs in a randomized controlled trial set-up for assessing mortality outcome in hypertension. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) Study did compare the two, but it was not a hypertension drug trial. The population it studied was high-risk CAD patients, rather than patients with left ventricular hypertrophy (LIFE).

**DIFFERENT MECHANISMS OF ACTION BETWEEN ACEI AND ARBS: COULD BE THE REASON?**

The ACEIs act by inhibiting the ACE enzyme and thereby preventing the formation of angiotensin II from angiotensin I and degradation of bradykinin. The inhibition of bradykinin degradation exerted by ACEIs is only considered an “adjunctive” mechanism with a limited clinical significance. But, if we consider the potential beneficial effect of bradykinin on the cardiovascular system, it is plausible that this pathway could possibly be responsible for many effects...
of ACEIs usually attributed to RAAS blockade. In hypertensive patients, bradykinin can act on the endothelium by a nitric oxide (NO)-dependent pathway, conceivably by the activation of endothelium-derived hyperpolarizing factors. Through this compensatory mechanism, bradykinin can induce endothelium-dependent relaxation or tissue plasminogen activator release, even in the presence of impaired NO availability, an effect not shared by other endothelial agonists, including acetylcholine. Therefore, the results of the comparative studies discussed earlier in patients with hypertension or CAD, ACEIs, but not ARBs can improve endothelial function in large arteries.

When ARBs were first introduced into clinical practice they were expected to lead to at least similar, if not greater, blood pressure lowering effects than ACEIs. Angiotensin receptor blockers act via a selective blockade of the angiotensin II type 1 receptor (AT-I), leaving the other angiotensin receptors (such as AT-II) relatively unchallenged. Importantly, as a consequence of the AT1 receptor blockade by ARBs, angiotensin II levels increase...
several fold through uncoupling of the negative feedback mechanism. The increased levels of angiotensin II leads to unrestricted stimulation of unopposed AT2 receptors. Although there are some mechanisms which has been proposed, stating that the stimulation of AT2 receptors mediates vasodilatation and NO release,18 which would be potentially beneficial, more recent evidence suggest that AT2 stimulation may actually lead to the stimulation of vascular growth, inflammation and fibrosis.19 In an experimental study, overexpression of the AT2 receptor in human cardiac myocytes lead to cardiac hypertrophy,20 whereas AT2 receptor-deficient mice appear to be protected against cardiac hypertrophy.21

To conclude, as recommended by recent international hypertension guidelines, the primary goal of treating hypertension must be aimed at maximum reduction in cardiovascular morbidity and total mortality2 and not just surrogates, such as BP and proteinuria. Special attention should be given to the choice of agent in high-risk hypertensive patients.

Presently, the evidence from hypertension trials clearly suggest that there is less risk of death with ACEI than ARB in hypertensive patients at low-risk of CAD (with lisinopril), at high-risk of CAD (with perindopril) and in the elderly (with perindopril). Even among the ACEIs the maximum evidence for reducing hard end points in hypertensive population seems to be in favor of perindopril with ASCOT, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and HYVET studies. What is interesting to note is that the most commonly used ACEI (ramipril) in India does not have a study in hypertensive population.

In addition to these clear outcome studies, the logical mechanisms which favorably differentiate an ACEI from an ARB have to be considered. Angiotensin-converting enzyme inhibitors should, therefore, be preferred to ARB in the treatment of hypertension as a first line treatment. As pointed out by guidelines,2 ARBs should be reserved for individuals who do not tolerate an ACEI.

REFERENCES