CHAPTER

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Role of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Hypertension 2017

Santosh Bandopant Salagre

INTRODUCTION

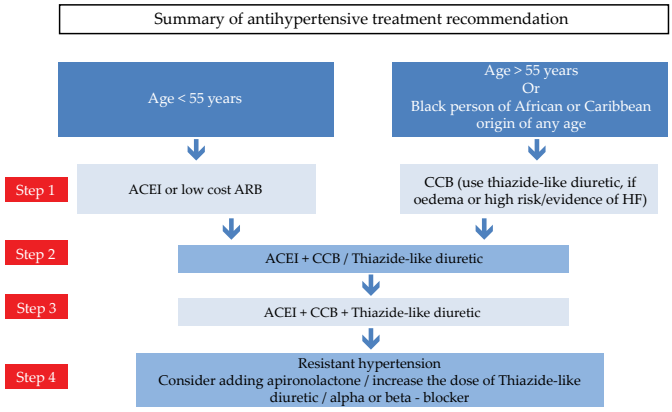
After the Framingham study first established hypertension as a risk factor of coronary artery disease, the objective of treating hypertension, as recommended by various hypertension guidelines, has been to reduce cardiovascular morbidity and mortality. Worldwide, annually 7.5 million deaths (13% of all deaths) are attributable to high blood pressure (BP)-related diseases, particularly cardiovascular diseases (CVD).

Angiotensin Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) are generally recommended by major hypertension guidelines as a first line of treatment, more so for younger, white hypertensive patients (below 55 or 60 years of age) in whom renin tends to be higher and Calcium Channel Blockers and Diuretics are more effective in old or black persons, in whom renin levels are generally lower.

As reflected in the flow chart (Figure 1), A refers to drugs that interrupt the renin-angiotensin system (ACEIs/ ARBs/renin inhibitor) and C and D refer to those that do not(calcium channel blockers and thiazide type diuretics). Combination of drugs from these groups is likely to be more potent in lowering blood pressure than combination within a group.

RENIN ANGIOTENSIN ALDOSTERON SYSTEM (RAAS) AND IT'S ROLE IN PATHOPHYSIOLOGY

The RAAS represents a cascade of enzymatic reactions. The huge precursor molecule of Angiotensin II (Ang II), Angiotensinogen, is cleaved by renin, resulting in the still inactive decapeptide angiotensin I (Ang I), which is then further cleaved by the membrane-bound metalloproteinase angiotensin-converting enzyme (ACE) to give the main effector hormone of RAAS, Ang II. Ang II is a known vasoconstrictor, causes fluid retention & has direct tissue toxic effects on vasculature, heart, brain & kidney. Ang II leads to CV damage by cell growth, inflammation & fibrosis, leading to vascular remodelling & endothelial dysfunction. Ang II also causes breakdown of bradykinin, an important mediator of ischemic preconditioning, endothelial function & fibrinolysis, important for CV protection.



Adapted from NICE-BHS hypertension guidelines 2011

Fig. 1: Flowchart of drugs inhibiting RAAS

ACEIS & ARBS – DO THEY ACT DIFFERENTLY?

While ACEIs act by reducing the production of Ang II, ARBs block the action of Ang II on AT_1 receptors, and hence act differently. ACEIs correct all the changes caused by Ang II and have thus demonstrated cardiovascular protection in addition to the BP control (Figure 2). In contrast, ARBs do not up-regulate bradykinin thus lacking the potential CV protective benefits associated with it. Also, since ARBs only block the AT_1 receptors, it leads to inhibition of negative feedback loop resulting in increase in Ang II levels by 200% to 300% from baseline. This increased Ang II stimulates AT_2 receptors, which in diseased coronary arteries, may lead to plaque rupture (Figure 3), myocardial infarction and adverse vascular remodelling. This could minimize or even negate the potential CV benefit of BP lowering via AT_1 receptor blockade.

ACEIS VS ARBS IN HYPERTENSION MANAGEMENT

Despite being in clinical use for many years, there has been no head to head comparison between angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) in a randomised controlled trial set up for assessing mortality outcome in hypertension. The 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 that of hypertension (large proportions were normotensive). Still, it is because of ONTARGET, that the ARBs have the perception of being equivalent to ACEIs in terms of CV events reduction.

ONTARGET compared telmisartan 80 mg (long acting ARB) to ramipril 10 mg (short acting ACEI, given at night in HOPE study to take care of early morning blood pressure

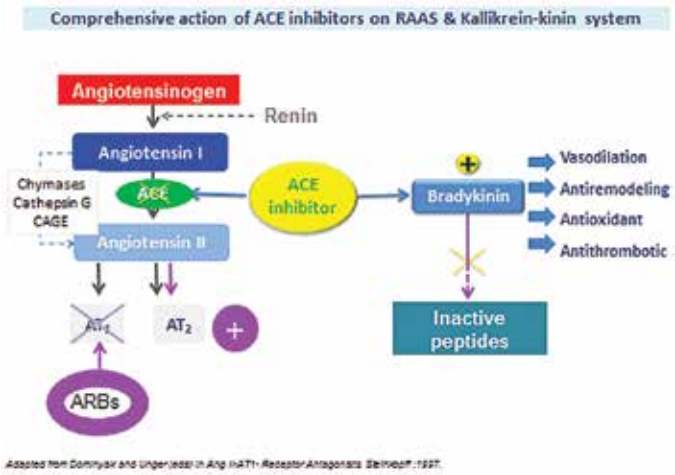


Fig. 2: ACE Inhibitors: A complete Mode of Action on RAAS and Kallikrein-Kinin System

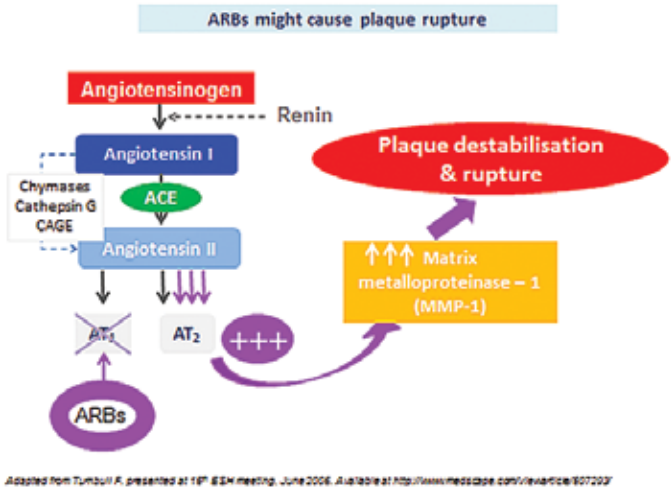


Fig. 3: ARBs migh cause Plaques Rupture

surges), both given once daily in the morning. There was no difference between groups in primary end point (composite of CV death, MI, stroke, hospitalization for HF, HR=1.01, 95% CI 0.94-1.09) or for all-cause mortality (HR=0.98, 95% CI 0.90-1.07). Patients on telmisartan had a lower BP (0.9/0.6 mmHg) & hence 9% lower risk of stroke, but the risk of MI was increased by 7% when compared to ramipril, consistent with the results of other studies and meta-analyses.

Though ONTARGET was designed and powered to be a 'superiority' trial, at best it could show the 'non-inferiority' of telmisartan, which statistically means, that telmisartan is not 'substantially worse' than ramipril. This led to USFDA approval to telmisartan as a 2nd line therapy for high risk patients who are ACEI intolerant.

CLINICAL UTILITY OF ACEIS & ARBS

ACEIs are the agents of choice in persons with type I diabetes with frank proteinuria or evidence of kidney dysfunction because they delay the progression to end-stage kidney disease. ACEIs may also delay the progression of nondiabetic kidney disease. The HOPE trial demonstrated that ramipril reduced the number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes. It also reduced the incidence of new-onset heart failure, kidney dysfunction, and new-onset diabetes in a population of patients at high risk for vascular events. ACEIs are drug of choice (usually in conjunction with a diuretic and a beta-blocker) in patients with reduced ejection fraction.

A meta-analysis of 20 trials involving ACEIs and ARBs, all done after the year 2000 in predominantly (two-thirds) hypertensive patients (7 ACEI trials, n=76615, 13 ARB trials, n=82383 patients) was published recently. Patients had similar co-morbidities and background treatments, etc. With a 4.3 years average follow up, there was a significant 5% (p-0.05) reduction in all-cause mortality with either an ACEI or an ARB. An independent analysis showed that ACEIs reduced all-cause mortality by 10% (p=0.004), while ARBs were neutral (HR=0.99, p=0.683). So the mortality reduction in the combined analysis was driven by the ACEI trials. Only 19% patients in the ACEI trials had placebo as a comparator, while in the ARB trials, 51% patients had a placebo as a comparator. As BP differential would be more in trials with a placebo comparator than with an active drug as a comparator, ARB trials should have shown better mortality reduction.

SAFETY PROFILE OF ACEIS AND ARBS

A chronic dry cough is common, seen in 10% of patients or more, and may require stopping of the drug. Skin rashes are observed with any ACEIs. Angioedema is an uncommon but potentially dangerous side effect because of their inhibition of kininase. Exposure of the fetus to ACEIs during second & third trimesters of pregnancy has been associated with defects due to hypotension and reduced renal blood flow. Severe hypotension can occur in patients with bilateral renal artery stenosis; sudden increase in Creatinine may ensue but are usually reversible with discontinuation of ACE inhibition. Hyperkalemia may develop in patients with kidney disease and type IV renal tubular acidosis (commonly seen in diabetics) and in the elderly.

Unlike ACE inhibitors, the ARBs do not cause cough and are less likely to be associated with skin rashes or angioedema. However, as seen with ACEIs, hyperkalemia can be a problem, and patients with bilateral renal artery stenosis may exhibit hypotension and worsened kidney function. Olmesartan has been linked to a sprue-like syndrome, presenting with abdominal pain, weight loss, and nausea, which subsides upon drug discontinuation.

CONCLUSIONS

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

Presently, the evidence from hypertension trials clearly & consistently suggests that there is less risk of death &

MI with ACEIs than the ARBs in hypertensive patients, which is over & above and "independent" of BP lowering.

Now if one looks at studies independently, five outcome trials in hypertension have compared ACEI with other agents. In ALLHAT (lisinopril vs. diuretic or calcium antagonist [CCB]); ANBP (enalapril vs. diuretic); ASCOT (perindopril and CCB vs. beta-blocker and diuretic); HYVET (perindopril and indapamide vs. placebo); and ACCOMPLISH (benazepril + diuretic vs. benazepril + CCB). ARBs have been compared with other agents in LIFE (losartan vs. atenolol); and VALUE (valsartan vs. amlodipine). This distribution of trial evidence suggests a greater quantum of evidence backing ACEI than ARB in the treatment of hypertension.

Even Among the ACEIs, the maximum evidence for reducing hard end points in hypertensive population seems to be in favor of Perindopril with ASCOT, 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. The trials or *statistical non-inferiority* should not be interpreted as *equivalence* trials. ACEIs should therefore be preferred to ARBs in the treatment of hypertension as a first line treatment. As pointed out by the guidelines ARBs should be reserved for individuals who do not tolerate an ACEI.

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