Inhibition of the Renin Angiotensin Aldosterone System – ACE Inhibitors or ARB for Cardiovascular Protection

Dr. Martin H. Strauss MD, FRCP(C), FACC

Activation of the renin angiotensin aldosterone system (RAAS) plays an important role in the pathophysiology of hypertension. Inhibition of the RAAS – either with an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) – lowers blood pressure effectively. ACEi and ARB reduce the risk of stroke, progression of diabetic renal disease, improve symptoms of congestive heart failure, and may – at least in post hoc analyses in large clinical trials – reduce the risk of new onset atrial fibrillation and diabetes mellitus[1]. ACEi also have a robust risk reduction in myocardial infarction and death in high risk patients, not only secondary to their anti-hypertensive effects, but above and "independent" of blood pressure lowering[1]. Two unique mechanisms may account for the blood pressure "independent" benefits of ACEi: 1) suppression of angiotensin II that has direct tissue toxicity independent of elevating blood pressure, 2) up regulation of bradykinin that potentiates ischemic preconditioning, fibrinolysis, and endothelial function – all providing cardiovascular protection[1].

ARB in contrast to ACEi, have shown little or no risk reduction in myocardial infarction or death in clinical trials. The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) have confirmed that ARB lack the unique blood pressure "independent" benefits of ACEi[2]. Furthermore, recent meta-analyses of ARB vs. placebo clinical trials – where placebo is the true measure of drug efficacy – have consistently demonstrated that ARB do not reduce the risk of myocardial infarction or death[3-5]. ARB lack of cardiovascular protection appears evident despite significant reductions in the risk of stroke[3-5] – with stroke being an endpoint that is highly dependent on blood pressure lowering. ARB lack of cardiovascular protection as compared to ACEi, despite similar blood pressure lowering, is referred to as the "ARB-MI Paradox" [1].

In a meta-analysis of 20 contemporary hypertension trials published since 2000 (n=158,998), where an ACEi or an ARB was compared to another agent - either another active comparator or a placebo - ACEi

reduced the relative risk in all cause mortality by 10% (p=0.004), whereas ARB only 1% (p=0.68)[6] which was not statistically significant. The divergent impact of these 2 RAAS inhibitors on all cause mortality does not appear to be secondary to a greater blood pressure lowering within the ACEi trials as compared to the ARB trials. In the ACEi trials only 19% of the patients had a placebo as the comparator whereas in the ARB trials, 51% of the patients had a placebo comparator – as blood pressure differential would be greatest in trials with a placebo comparator as compared to another active comparator, blood pressure lowering would have favored mortality reductions in the ARB trials.

The evidence within the clinical trials supports the conclusion that ACE inhibitors should be considered preferential treatment over an ARB for cardiovascular protection.

Reference List

(1) Strauss MH, Hall AS. Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox. Circulation 2006; 114(8):838-854.

(2) Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. J Hypertens 2007; 25(5):951-958.

(3) Savarese G, Costanzo P, Cleland JG, Vassallo E, Ruggiero D, Rosano G et al. A meta-analysis reporting effects of Angiotensin-converting enzyme inhibitors and Angiotensin receptor blockers in patients without heart failure. J Am Coll Cardiol 2013; 61(2):131-142.

(4) Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ 2011; 342:d2234.

(5) Elgendy IY, Huo T, Chik V, Pepine CJ, Bavry AA. Efficacy and Safety of Angiotensin Receptor Blockers in Older Patients: A Meta-Analysis of Randomized Trials. Am J Hypertens 2014.

(6) van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. Eur Heart J 2012; 33(16):2088-2097.