EDITORIAL

Angiotensin receptor blockers in patients with heart failure and a reduced left ventricular ejection fraction

Implications of the HEAAL trial

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Angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective in reducing mortality and hospitalization in patients with heart failure (HF) and a reduced left ventricular ejection fraction (LVEF).[1,2] Angiotensin receptor blockers (ARBs) have been directly compared to ACE inhibitors in patients with chronic HF and a reduced LVEF and in patients with HF or reduced LVEF post myocardial infarction and appear to be as effective in reducing mortality and hospitalization for HF as ACE inhibitors,[3-5] but are better tolerated. ACE inhibitors, however, remain the choice to inhibit the effects of angiotensin II (AT II) in patients with HF and a reduced LVEF[6] in large part due to the fact that several of the ACE inhibitors, shown to be effective in these patients, are generic and therefore relatively inexpensive. An increasing number of ARBs are or soon will be generic with a resultant reduction in their cost differential. The recent results of the HEAAL study (Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan)[7] in over 3800 patients with HF and a reduced LVEF who were intolerant to an ACE inhibitor and were randomized to losartan either at a dose of 50 mg or 150 mg daily demonstrating that the 150 mg dose of losartan was more effective than the 50 mg dose, the dose used in 2 of the major comparative trials of ACE inhibitors and ARBs (ELITE II [the Evaluation of Losartan in the Elderly][3] and OPTIMAAL [Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan])[4] in reducing mortality and hospitalization for HF are therefore of interest for a number of reasons including the need to reconsider the comparative effectiveness of ACE inhibitors and ARBs in patients with HF and a reduced LVEF.

First, the results of the HEALL study call into question the results of the prior ACE inhibitor vs. ARB comparative trials such as ELITE II[3] and OPTIMAAL.[4] The 50 mg dose of losartan used in these trials was selected based upon the fact that this was the most common dose used at the time for patients with hypertension rather than on the basis of careful dose response studies in patients with HF and a reduced LVEF. The results of VALIANT (Valsartan in Acute Myocardial Infarction Trial)[5] in which valsartan at a dose of 160 mg twice daily was compared to captopril at a target dose of 50 mg 3 times a day may also be questioned since a 640 mg dose of valsartan has been shown to be more effective than lower doses in reducing albuminuria.[8]

Given the results of HEAAL[7] one might postulate that the results of the prior ACE inhibitor vs. ARB comparative trials[3-5] might have been different, had a higher dose of an ARB, such as losartan 150 mg, been used. Regardless of the outcome of future direct comparative trials of ACE inhibitors and ARBs in patients with HF and a reduced LVEF, the results of HEAAL[7] suggest that the use of losartan at a dose of 50 mg daily in these patients has resulted in the loss of many lives and many unnecessary admissions to the hospital. These results also have implications for our understanding of the relative importance of various mechanisms associated with inhibition/blockade of the renin-angiotensin-aldosterone (RAA) system. There has been speculation that blockade of the AT II type 1 receptor might be a more effective means of preventing the adverse effects of AT II than inhibiting the conversion of AT I to AT II by blocking both ACE dependent and independent formation of

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AT II. Similarly, some have speculated that unopposed stimulation of the AT type 2 receptor might be beneficial in increasing nitric oxide (NO) availability. The results of the prior ACE inhibitor vs. ARB comparative trials which failed to demonstrate a superiority of ARBs[3-5] have led to the speculation that other mechanisms, such as ACE inhibitor-induced bradykinin formation or the formation of angiotensin-(1-7) might be as or more important for cardiovascular protection. Should future direct comparative trials of ACE inhibitors to high-dose ARBs yield results different than the prior comparative trials,[3-5] the relative importance of these mechanisms might need to be reconsidered.

The finding that a 150 mg dose of losartan is more effective in reducing cardiovascular events in patients with HF and a reduced LVEF than a 50 mg dose may also have important implications for patients with hypertension and other cardiovascular diseases. Losartan has often been perceived as a relatively weak antihypertensive agent in comparison to other ARBs, in large part due to the fact that it is most often used at a dose of 50–100 mg daily alone and/or in conjunction with hydrochlorothiazide. While there may be only a relatively small incremental effect on blood pressure as the dose of losartan is increased from 50–100 mg to 150 mg daily, there may be other cardiovascular effects that may be of importance in determining target organ protection and cardiovascular events in patients with hypertension that may have a different dose response than blood pressure per se. There is increasing evidence that while blood pressure lowering is important in the therapy of patients with hypertension, there may be blood pressure independent effects that may be as or more important in reducing cardiovascular events. For example, in the ACCOMPLISH trial (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension)[9] in patients with high-risk hypertension, the combination of benazapril/amlodipine was more effective in reducing major cardiovascular events than the combination of benazapril/hydrochlorthiazide at a similar blood pressure reduction. Despite several decades of clinical investigation with both ACE inhibitors and ARBs we have a rather incomplete understanding of the dose-response relationship of these agents on a number of important cardiovascular parameters such as NO availability, inflammatory cytokine activation, immune responses, myocardial and vascular hypertrophy, and renal function. All too often, the dose that is thought optimum in regard to blood pressure lowering is chosen for clinical use without regard to the real goal in treating patients with hypertension, i.e., preservation of target organs and a reduction in cardiovascular events. Furthermore, while 150 mg of losartan has been shown to be more effective than 50 mg in patients with HF and a reduced LVEF, there is a suggestion that even higher doses such as 100 mg twice daily might be even more effective.[10]

While a 150 mg daily dose of losartan appears to be more effective than 50 mg[7] in patients with HF and a reduced LVEF, it would be prudent to slowly up titrate to the higher dose in view of the fact that the higher dose is associated with an increased incidence of adverse effects including hypotension, renal dysfunction, and hyperkalemia. The incidence of these events in clinical practice might have been underestimated by the fact that patients in HEAAL[7] were shown to be tolerant to losartan during a run in period prior to being randomized to the 150 and 50 mg dosing strategy. Increasing evidence suggests that hypotension may have adverse consequences on cardiovascular events in patients with HF[11,12] especially in the very old (>75 years of age), in whom there is an increased incidence of concomitant atherosclerosis in the cerebral and renal arteries and therefore the risk of inducing ischemia and infarction.

In conclusion, HEAAL[7] points out that despite several decades of clinical investigation into the use of ACE inhibitors and ARBs in patients with HF and a reduced LVEF our understanding of the RAA system and the best strategy to inhibit/block the effects of AT II remains incomplete. While ACE inhibitors remain the choice in patients with chronic HF and a reduced LVEF, the results of HEAAL[7] emphasize the need to more fully understand the dose response of ACE inhibitors, ARBs, and other new drugs for the therapy of HF on a number of parameters important in the pathophysiology of HF before embarking on large-scale outcome trials and should prompt further investigation into the most effective means to reduce the still unacceptably high mortality and incidence of hospitalization for HF in these patients.

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