Controversies in the pharmacologic therapy of patients with heart failure

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Current evidence suggests that all patients with chronic heart failure (HF) and systolic left ventricular dysfunction (SLVD) should be treated with an angiotensin converting enzyme –inhibitor (ACE-I) and a beta adrenergic blocking agent (BB) to reduce cardiovascular (CV) mortality and hospitalization for HF , unless contraindicated or not tolerated (1). Most patients with chronic HF and SLVD will also require a diuretic. However , the role of diuretics , especially non potassium sparing diurectics (NPSDs) is controversial since a retrospective analysis of the studies of left ventricular dysfunction (SOLVD) has suggested that the use of NPSDs is associated with an increased risk of death due to progressive HF and sudden cardiac death (SCD) in comparison to patients not requiring a diuretic and those using a potassium sparring diuretic (PSD) (2) . This finding while scientifically plausible due to the effect of NPSDs on the Renin – Angiotensin– Aldosterone System (RAAS) and the loss of potassium, which is cardio-protective, is however confounded by selection bias in that patients requiring NPSDs may be sicker than those not on a diurectic or on a PSD .The role of digoxin in patients with chronic HF and SLVD is also controversial. In the DIG trial (3) the addition of digoxin to standard therapy including an ACE-I , BB , and a diurectic failed to demonstrate a reduction in CV mortality but did show a significant reduction in hospitalization for HF . The lack of benefit on CV mortality has led to a decrease in the use of digoxin in patients with chronic HF and SLVD . A retrospective analysis of the DIG trial suggests however that in those patients in whom the serum digoxin level is maintained between 0.5 and 1.0 micro grams /ml that there may be a beneficial effect on CV mortality (4). Patients with chronic HF and SLVD due to ischemic heart disease will also often be treated with a statin , although the evidence from prospective large scale randomized trials in this situation is lacking but currently under investigation . The role of statins in patients with HF and SLVD due to non ischemic cardiomyopathy is even more controversial since some small randomized studies have shown a benefit on various surrogate endpoints while others have not (5,6,7) . Thus, the role of NPSDs , digoxin , and statins will require further prospective evaluation in large scale randomized trials to determine their role in the current therapy of HF and SLVD .

In patients with chronic HF and SLVD who have symptoms or signs of progressive HF despite therapy with an ACE-I , BB , +/- a NPSD, digoxin , and a statin there is also controversy as to what

additional pharmacologic therapy should be added . Two major pharmacologic strategies have been evaluated in patients with chronic HF and SLVD treated with an ACE-I and a BB. One strategy is the use of an angiotensin receptor blocking agent (ARB) in addition to an ACE-I and a BB and the other the use of an aldosterone blocker (AB). There are currently no prospective randomized trials comparing these two strategies. There is however considerable experience with each , which can provide some insight into their choice.

The rationale for the addition of an ARB to an ACE-I in patients with HF and SLVD is based upon the observation that ACE-Is may not completely prevent the formation of angiotensin II due to the presence of non-ACE dependent enzymes for forming angiotensin II , such as chymase .Two large scale randomized trials have explored the strategy of adding an ARB to an ACE-I in patients with chronic HF and SLVD , the Val-Heft (8) and Charm added trial (9) . In Val-Heft (8) the addition of the ARB valsartan to patients treated with an ACE-I and a BB failed to demonstrate any significant reduction in CV mortality, although there was a significant reduction in hospitalization for HF . However, even this benefit appeared to be lost when patients who were on optimum or target doses of their ACE-I were analyzed. In contrast in the Charm –added trial (9) the addition of the ARB candesartan to an ACE-I resulted in a significant benefit in the combined endpoint of CV mortality and hospitalization for HF. Retrospective analysis of these results in patients on optimum or target doses of their ACE-I suggests that the addition of candesartan remains beneficial. The explanation for the difference in results in Val-Heft (8) and Charm –added (9) is uncertain but could be related to patient selection , differences in effectiveness of valsartan and candesartan , although there is no convincing evidence to indicate that candesartan is superior to valsartan in patients with HF at the doses used , or chance . The role of adding an ARB to an ACE-I in patients with HF and SLVD is further clouded by the finding in the Valiant trial (10) in patients with HF post MI in which the addition of the ARB , valsartan , to an ACE-I , captopril , failed to show any benefit in regard to CV mortality or hospitalization for HF but was associated with an increase in adverse events . This trial did however demonstrate that a strategy of an ARB was equivalent to an ACE-I . Thus, while ARBs may be equivalent to an ACE-I the evidence for their benefit when added to an ACE-I at target or optimum doses in patients with HF and SLVD is inconclusive in regard to CV mortality.

The role of AB in patients with chronic HF and SLVD treated with standard therapy including an ACE-I and a BB is evolving .The Rales trial (11) in which patients with severe HF and SLVD treated with standard therapy were randomized to the AB spironolactone at dose of 25-50 mg daily or placebo demonstrated a significant 30% reduction in all cause mortality in patients treated with

the AB. The reduction in total mortality was due both to a reduction in death due to progressive HF as well as SCD. In addition there was a 35% reduction in hospitalization for HF. These beneficial results were seen across a variety of pre-specified sub groups including age, gender and etiology of HF. On the basis of this trial AB have been recommended in both the AHA/ ACC and European Heart Association guidelines for patients with severe HF and SLVD.

The rationale for the use of an AB in addition to an ACE-I in patients with HF and SLVD is based upon the finding that although angiotensin II is a potent stimulus for the adrenal production of aldosterone other stimuli such as serum potassium may in certain circumstances be as or more important. For example, in angiotensinogen knock out mice, in which there is no angiotensin II , aldosterone can still be released from the adrenal gland by altering serum electrolytes (12). Thus, regardless of the use of an ACE-I and or an ARB aldosterone production from the adrenal gland persists. Furthermore, aldosterone has proven far more important in CV pathophysiology than previously thought. Aldosterone by stimulating the mineralo-corticoid receptor (MR) in the distal renal tubule causes sodium retention and potassium loss. More recently however MR have been identified in the myocardium , endothelium , brain , and other organs (13) and have been shown to have a number of effects when stimulated including : myocardial and vascular hypertrophy and fibrosis , vascular inflammation , endothelial dysfunction , dysregulation of the autonomic nervous system , an increase in central sympathetic activity , activation of platelets , and an inhibition of fibrinolysis that are important in the pathophysiology of HF (14) . While MR may be stimulated by aldosterone they may also under circumstances of increased oxidative stress and down regulation of the enzyme 11 beta-hydroxy steroid dehydrogenase - 2(11B-HSD2) be stimulated by cortisone.

Although recommended for use in patients with severe HF and SLVD AB have not been recommended in patients with mild –moderate HF. There are however several small randomized trials showing a benefit of AB on various surrogate endpoints in patients with mild-moderate HF and SLVD treated with an ACE-I and a BB including : an improvement in ventricular remodeling , a decrease in collagen formation , an improvement in endothelial function and exercise tolerance which appear promising . A large scale prospective randomized study of patients with HF and SLVD in NYHA class II HF is planned to begin shortly and will compare the AB eplerenone to placebo in regard to the combined endpoint of CV mortality and hospitalization for HF. Eplerenone blocks the MR but is more specific than spironolactone and therefore does not have the well known side effects associated with spironolactone such as gynechomastia , breast pain and impotence in males, resulting from down regulation of androgen receptors, or menstrual

irregularities and libido changes in pre-menstrual females , resulting from up-regulation of progesterone receptors .

The extrapolation of the results of AB in Rales (11) to patients with mild –moderate HF has been questioned since in Rales only 10-11% of patients were on a BB in addition to an ACE-I , since the trial was carried out before the results of BB in patients with severe HF were known . However as mentioned above small randomized trials using surrogate endpoints have demonstrated a beneficial effect of AB in patients with mild-moderate HF and SLVD treated with both an ACE-I and a BB . Furthermore , in the Ephesus trial (15) in which the AB eplerenone or placebo was randomized in patients with HF and SLVD post MI , most of whom were treated with both an ACE-I and a BB, eplerenone was shown to have a beneficial effect on total mortality . An analysis of patients treated with both an ACE-I and a BB in Ephesus shows an even greater benefit on mortality than overall. Of interest , in Ephesus (15) patients treated with optimum therapy including aspirin , a statin , reperfusion , a diuretic , an ACE-I or ARB , and a BB showed a benefit of eplerenone on total mortality , suggesting that AB provides additional benefit above and beyond current therapy . Also of interest was the finding that in patients with the lowest quartile of systolic blood pressure (SBP) at baseline that eplerenone when added to standard therapy did not result in a drop in SBP compared to placebo early post MI , whereas in the quartile with the highest SBP both eplerenone and placebo similarly reduced SBP. .This suggests an important safety advantage of an AB in comparison to an ARB when added to an ACE-I since when an ARB is added to an ACE-I in patients with HF and SLVD there is a mean 3-6 mm Hg drop in systolic blood pressure. In patients with chronic HF and SLVD as well as in patients with HF post MI a fall in systolic blood pressure of this magnitude may be detrimental and could lead to myocardial ischemia, myocardial cell death, and further left ventricular dysfunction (16).

While the results of the Rales and Ephesus trials (11,15) demonstrate a significant benefit of an AB when added to an ACE-I on total mortality many clinicians have been reluctant to adopt this strategy due to the fear of inducing serious hyperkalemia . However, in both the Rales (11) and Ephesus (15) trials the risk of serious hyperkalemia (serum potassium > 6.0 meq/l) was low and there were no deaths attributable to hyperkalemia in patients randomized to the AB . Nevertheless, there have been reports since the publication of Rales (11) pointing out a relatively high incidence of hyperkalemia in patients treated with HF and SLVD with an AB in clinical practice (17). The use of an AB in these studies, mainly spironolactone , was associated with an increase in renal failure , occasionally requiring dialysis , and death . The greater incidence of serious hyperkalemia and adverse events noted when an AB was used in clinical practice rather than in a clinical trial is of

concern. In Rales and Ephesus (11,15) patients were excluded from randomization if they had a serum potassium > 5.0 meq/l and or a serum creatinine > 2.5 mg/dl . In many of the patients shown to have serious hyperkalemia when using an AB in clinical practice these criteria were not met. Patients treated in clinical practice were also often older than those in the randomized trials and therefore their serum creatinine may not have reflected the extent of their renal dysfunction. AB should not be used in patients with an estimated creatinine clearance (CrCl) < 30 ml/min .In those patients with a CrCl > 30 but < 60 ml /min serum potassium should be closely monitored . In the Rales trial (11) serum potassium was monitored at baseline, within 1 week of starting spironolactone , at 1 month and then every 3-6 months thereafter . If at any time serum potassium is > 5.5 meq/l the dose of AB should be reduced by half and if > or = to 6.0 meq/l on a non hemolyzed sample it should be withheld, at least temporarily. Any time a patient has a condition altering serum electrolytes such as vomiting or diarrhea or when a drug resulting in potential potassium retention, such as an NSAID, is added serum potassium should be re-monitored and or the dose of AB withheld until it is monitored. Evidence from both the Rales and Ephesus trials (11,15) in over 4000 patients with HF and SLVD treated with an AB suggests that when appropriate inclusion and exclusion criteria are used , potassium monitored , and the dose of AB adjusted if necessary , that an AB when added to an ACE-I is safe and associated with a significant reduction in total mortality .

While current evidence suggests that either an ARB or an AB when added to an ACE-I may be beneficial in a patient with chronic HF and SLVD there is as yet , as pointed out above, no direct comparison of these two strategies . Thus, individual clinicians will need to choose between them based upon their interpretation of current evidence .The role of either an ARB or an AB added to an ACE-I is further complicated by the increasing use of cardiac resynchronization therapy (CRT) (18) and or automatic implanted cardiac defibrillators (AICD) (18) in patients with HF and SLVD and the lack of adequately designed randomized trials to define their relative roles in comparison to an ARB or AB in patients treated with an ACE-I and a BB . In patients with HF and SLVD post MI the choice is however clear in view of the failure of an ARB to provide any additional benefit when added to an ACE-I (10) and the lack of benefit of an AICD when implanted early post MI (20) . It is however likely that over the next several years that an ARB will be compared to an AB in patients with HF and SLVD treated with an ACE-I and a BB and that the role of AB in patients with HF will increase beyond severe chronic HF and HF post MI and SLVD . As mentioned above the AB eplerenone will be studied in a large randomized placebo controlled trial in patients with NYHA class II HF and SLVD. There is also a large scale placebo controlled trial of the AB

spironolactone in patients with HF and preserved systolic left ventricular function (PSF) that will begin this year under the auspices of the NHLBI. Current therapy of patients with HF and PSF is uncertain, since there is as yet no clear evidence from randomized trials as to the benefit of any single agent. For example, in the Charm-preserved trial (21) the addition of the ARB candesartan to standard therapy often involving a diuretic, BB, and or a calcium channel blocker was equivocal. While our understanding of the pathophysiology of HF due to PSF is incomplete it appears that hypertrophy and fibrosis of the myocardium and major vessels due to age, hypertension, and often atherosclerosis are important. AB have been shown to reduce blood pressure in patients with resistant hypertension , ie patients in whom blood pressure goal has not been accomplished with three or more standard antihypertensive agents at target or maximally tolerated doses , to reduce left ventricular mass ,and decrease vascular stiffness . In a small randomized trial in patients with diastolic HF AB has been shown to improve doppler echocardiograpic indices of diastolic function (22). AB has also been shown to improve the extent of experimental atherosclerosis. However, until the results of the randomized trials of AB in patients with NYHA class II HF and SLVD and in patients with HF and PSF are known it would be prudent to restrict the use of AB to those patients with severe or progressive HF and SLVD and to those with HF and SLVD post MI.

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