1. ALDO-DHF STUDY – A NEW INDICATION FOR AN OLD DRUG?

Results of the ALDOsterone receptor blockade in Diastolic Heart Failure (ALDO-DHF) were recently presented at the European Society of Cardiology (ESC) meeting in Munich [1]. The multicenter, double-blind randomized, placebo-controlled phase IIb mechanistic study was conducted to test the hypothesis that 12 months treatment with spironolactone would improve cardiac function and structure as well as exercise capacity and quality of life in patients with heart failure with preserved ejection fraction (HFrEF). HFrEF continues to be a challenging form of heart failure – one in which no therapy has yet been proven to improve outcome and with a prevalence that continues to rise at an alarming rate. An extensive review on HFrEF – including various drugs in current use as well as those under trial – was published in the last issue of the journal [2].

The study randomized 422 patients with HFrEF to spironolactone 25 mg/day or placebo on top of other medical therapy and was funded by the German government within the Clinical Trial Research Program. The two co-primary endpoints were changes in diastolic function (assessed by tissue-Doppler derived E/e0 – a validated echocardiographic marker of left ventricular filling pressures) and changes in maximal exercise capacity (assessed by peak oxygen consumption – VO2 max – during bicycle spiroergometry). Secondary endpoints included left ventricular mass index (LVMI), quality of life, NYHA class and levels of N-terminal pro-brain-type natriuretic peptide (NT-proBNP) as a marker of neuroendocrine activity.

At one year, the group receiving spironolactone showed significant improvement in diastolic function (E/e0 – p < 0.001). There was significant reduction in LVMI (p = 0.009) and NT-proBNP levels (p = 0.03) in the spironolactone arm. Interestingly, changes in LV mass were independent of the modest blood pressure lowering effect that spironolactone had (mean 8/3 mmHg). These beneficial cardiac functional and structural changes did not, however, translate into clinical gains with spironolactone failing to improve peak exercise capacity, NYHA class or quality of life at 12 months compared placebo. There were no serious adverse events related to spironolactone but its use was associated with worsening renal function (36% with spironolactone and 21% with placebo – p < 0.001) and persistent elevation of serum potassium levels. In addition spironolactone carried a greater risk of new or worsening anemia compared to placebo (16% vs. 9% - p = 0.03) and gynecomastia (4% vs < 1% - p = 0.02). While presenting the results at the ESC meeting, the investigators concluded that “spironolactone can be considered in patients with diastolic heart failure for improving cardiac function and blood pressure control”.

The results of the study are difficult to interpret from the practicing physician’s point of view. Compared to “real life” HFrEF patient population, the patients recruited in this study were relatively younger (mean age = 67 years), had lower NT-proBNP values, lower rates of atrial fibrillation (4%) and better baseline renal function (mean = 97 ml/min/1.73m2). These features, together with the fact that only 15% of patients had more than NYHA class II symptoms, raise some concerns as to whether the study population truly represents the broader HFrEF population. The lack of symptomatic improvement in the active treatment arm might be related to these baseline patient characteristics which probably represent the mild end of the spectrum of HFrEF. The results also highlight the complex and multifactorial cause of symptoms in HFrEF where a number of pathophysiological features – beyond diastolic dysfunction – interact to produce symptoms as previously shown in a number of studies [2,3].
What have we learned?

All put together, results of ALDO-DHF – while being very interesting from a mechanistic point of view – are unlikely to change clinical practice significantly given the lack of symptomatic improvement and potentially serious side effects associated with the use of spironolactone. At this stage, spironolactone can only be recommended as a third- or fourth-line antihypertensive agent in patients with HfPEF who have not achieved target blood pressures, and with close monitoring of renal function and serum potassium levels. More insight into the clinical value of spironolactone in HfPEF should be provided next year by the results of the Treatment of Preserved Cardiac Function Heart Failure (TOPCAT) study [4].

2. PARAMOUNT – THE NEW KID ON THE BLOCK

Results of another trial addressing treatment of HfPEF - The Prospective compArison of angiotensin Receptor/neprilysin inhibitor with Angiotensin receptor blocker on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial – were also presented at the European Society of Cardiology meeting in Munich [5,6].

PARAMOUNT was a phase II multicenter trial conducted in 13 countries that randomized 308 patients (mean age = 71 years with 57% being women) with a documented history of heart failure, ejection fraction of ≥ 45% and NT–proBNP ≥ 400 pg/ml to either the angiotensin receptor blocker valsartan or to the novel angiotensin receptor/neprilysin inhibitor (ARNI) – currently known as LCZ696. This first-in-class drug is a dual-acting neprilysin inhibitor and angiotensin receptor blocker as it comprises the molecular moieties of both AHU337 and valsartan. Neprilysin is an endopeptidase that degrades the biologically active natriuretic peptides including atrial natriuretic peptide (ANP), brain-type natriuretic peptide (BNP) and C-type natriuretic peptide. The biologically inert NT-proBNP is not a substrate of this enzyme and is therefore unaffected by its inhibition i.e. changes in circulating levels reflect true changes in left ventricular wall stress [7]. Natriuretic peptides have potent vasodilator and diuretic properties, reduce sympathetic drive, and have antiproliferative and antifibrotic effects. They also enhance myocardial relaxation via increasing the generation of cardiac cyclic guanosine monophosphate (cGMP) [8]. Neprilysin is however also involved in the breakdown of angiotensin II, hence the rationale for using dual-acting agents that combine neprilysin inhibition with angiotensin receptor blockage. The primary end-point was change from baseline NT-proBNP assessed at 12 weeks. Secondary end-points included changes in left ventricular volumes, ejection fraction, left atrial volume and echocardiographic parameters of diastolic function as well as NYHA class and quality of life (Kansas City Cardiomyopathy Questionnaire). The investigators postulated that cardiac structural changes will need more time to manifest, hence chose to assess them at 36 weeks.

At 12 weeks, change in NT-proBNP levels from baseline was significantly different in the LCZ696 group compared with the valsartan group (ratio of change LCZ696/valsartan 0.77, 95% CI 0.64–0.92, p = 0.005) with a greater reduction seen in the LCZ696 arm – a finding that remained significant after adjusting for changes in blood pressure. Prespecified subgroups analysis broke patients out by age, systolic blood pressure, atrial fibrillation, renal function and diabetes. The beneficial effect of LCZ696 on NT-proBNP remained statistically significant amongst each of these subgroups; however, it appeared to be more striking in diabetic patients. At 36 weeks, the difference between NT-proBNP levels in both groups was no longer significant (p = 0.20). Left atrial volume – a powerful prognostic indicator in patients with heart failure and an accurate marker of the chronicity of elevated left ventricular filling pressures – was significantly reduced in the LCZ696 group (p = 0.003). All other echocardiographic measurements did not differ between both treatment groups. Improvement in NYHA class (but not quality of life) was noted at 36 weeks in the LCZ696 group compared to the valsartan group. The number of patients with hypotension, renal dysfunction or hyperkalemia did not differ between groups. Estimated glomerular filtration rate (eGFR) decreased to a greater extent in the valsartan group (LCZ696, −1.6 mL/min per 1.73 m² vs valsartan, −5.2 mL/min per 1.73 m²; p = 0.007) and urinary albumin:creatinine ratio increased to a greater extent in the LCZ696 group (LCZ696, 1.9 mg/mmol at baseline, 2.9 mg/mmol at week 36; valsartan, 2.0 mg/mmol at baseline, 2.0 mg/mmol at week 36; p = 0.02). Adverse events did not differ significantly between both treatment groups; the study was not however designed to test clinical outcomes [6].
What have we learned?

The promising results of PARAMOUNT represent an important step towards the development of effective treatment for HFpEF and will almost certainly trigger a larger phase III trial powered to test clinical outcomes in the near future. Although some of the study’s findings remain difficult to interpret (e.g. failure to improve echocardiographic indices of diastolic function), the effect of LCZ696 on two powerful predictors of outcome in HFpEF – NTproBNP and left atrial volume – are extremely encouraging and warrant further testing in this patient population.

References


