

The mechanistic effects of spironolactone in diastolic heart failure

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Mineralocorticoid receptor antagonists should be considered as a treatment option in hypertensive patients with diastolic heart failure, said Professor Burkert Pieske presenting results today of the Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) study at ESC Congress 2012.

Behind his conclusion lay results showing that mineralocorticoid receptor blockade with spironolactone improves cardiac function and structure, reduces neuroendocrine activation, and effectively reduces blood pressure in a patient population with symptomatic predominantly hypertensive diastolic [heart failure](#). However, results also showed that spironolactone did not improve [exercise capacity](#) or symptoms of heart failure.

As background to the study Professor Pieske, Head of Cardiology at the Medical University Graz in Austria, explained that diastolic heart failure (DHF) - also known as heart failure with preserved [ejection fraction](#) - is a condition which increasingly affects millions of people in Europe. Today, he said, more than half of all [heart failure patients](#) have DHF, as opposed to classical [systolic heart failure](#), and DHF is the dominant form of heart failure in elderly patients, especially women. Patients suffer from poor quality of life, impaired exercise capacity and a high rate of hospitalisation and mortality.

"Mechanistically," said Professor Pieske, "the main underlying pathology is thought to be impaired filling of the [left ventricle](#), often as a

consequence of long-standing hypertension, diabetes, and other lifestyle-associated cardiovascular risks factors. However, despite the large number of affected patients and the poor outcome, no therapy has so far demonstrated [therapeutic benefit](#).

"The neuroendocrine hormone aldosterone mediates, through mineralocorticoid receptors, adverse effects on cardiac function and remodelling, as well as on vascular stiffness. In consequence, aldosterone induces myocardial hypertrophy, fibrosis and diastolic dysfunction, all potential mechanistic factors in the pathology of diastolic heart failure. However, despite this mechanistic evidence and convincing benefits in systolic heart failure, aldosterone antagonism has never been tested in a large randomised multicentre trial in patients with DHF."

The Aldo-DHF trial was designed to test the hypothesis that 12 months treatment with the mineralocorticoid receptor antagonist spironolactone would improve [cardiac function](#) and structure, as well as exercise capacity and quality of life in patients with DHF. The study was an international multicentre Phase IIb trial funded after peer review by the German government within the Clinical Trial Research Program.

Aldo-DHF prospectively randomised 422 patients with symptomatic DHF to either spironolactone (target dose, 25 mg/day) or placebo over a treatment period of 12 months. The two co-primary endpoints were changes in diastolic function (filling pressure, assessed non-invasively by tissue-Doppler derived E/e', an established and validated echocardiographic estimate of left ventricular filling pressure) and changes in maximal exercise capacity (peak oxygen consumption, VO₂), assessed by bicycle spiroergometry after 12 months.

Secondary endpoints included other parameters of echocardiographic functional and structural cardiac abnormalities, submaximal exercise capacity, quality of life and NYHA class. Safety including classical side

effects such as increase in serum potassium or decreases in renal function were also assessed.

Results showed that spironolactone significantly improved diastolic function (assessed as a significant decline in E/é), but did not change maximal exercise capacity (peak V02) after one year. Spironolactone also induced reverse cardiac remodelling and reduced left ventricular hypertrophy, a known detrimental consequence of hypertension and diabetes), NTproBNP plasma levels, and systolic and diastolic blood pressure.

However, spironolactone did not improve other measures of exercise capacity, NYHA class, or quality of life, but was shown to be safe, without relevant adverse events.

Results from the NIH-funded TOPCAT trial will show if these beneficial effects of spironolactone translate into better clinical outcome.

Provided by European Society of Cardiology

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