The risk of developing heart failure with reduced ejection fraction (HFrEF) in a patient with ischemic heart disease depends, mainly, of infarct size and post ischemic ventricular remodeling. Blockade of the renin-angiotensin-aldosterone system and the sympathetic nervous system have shown significant benefits reducing mortality and improving quality of life in this group of patients.

Recently, the combined use of an angiotensin receptor antagonist (valsartan) and a neprilisin inhibitor (sacubitril) was observed to be more effective than the inhibition of the renin-angiotensin-aldosterone system to reduce global morbidity and mortality of patients with HFrEF. The benefits of the combined administration of sacubitril/valsartan in patients with heart failure are attributed to the restitution of the neurohumoral equilibrium that takes place in the failing heart, thus having favorable effects on ventricular remodeling. Different preclinical studies support this theory through experimental studies, especially in small rodents. However, there are no studies analyzing the effects of using these drugs on acute myocardial infarction and its subsequent progress to heart failure.

In this interesting study, Torrado et al. explored the effects of the acute or chronic administration of the combined use of sacubitril/valsartan compared with valsartan alone in myocardial ischemia/reperfusion in rabbit models of myocardial infarction.

In the acute protocol, after 45 minutes of regional ischemia by anterior descending coronary artery occlusion, the hearts were reperfused for 72 hours before concluding the study. The administration of sacubitril/valsartan or valsartan at the onset of reperfusion reduced infarct size and troponin I levels in both groups, compared with the untreated control group. However, only the combined administration of sacubitril/valsartan improved ventricular function recovery assessed through the ejection fraction. In the chronic protocol, the experiments were followed-up for 10 weeks after reperfusion and the drugs were administered in two ways: from the onset of reperfusion or from week six onwards. In both situations, the significant reduction of infarct scar size was only observed in the group with combined treatment. Also, a lower reduction of ejection fraction was observed in the group that received early combined treatment and its recovery when treatment was administered from week six of evolution in animals with ejection fraction <40%. In conclusion, although both the combined treatment with sacubitril/valsartan as the treatment with valsartan alone are able to reduce acute infarct size, the combined treatment has additional benefits over valsartan monotherapy to prevent or improve the ventricular function impairment that accompanies post ischemic ventricular remodeling.

Recently, the PARADIGM-HF study demonstrated that the combined treatment with sacubitril/valsartan was superior to enalapril to reduce mortality and hospitalization of patients with heart failure, with the additional benefit that a lower percentage of patients presented renal involvement. These positive results prompted the approval by the FDA and the European Medical Agency for its use in patients with heart failure.

The study by Torrado et al. provides interesting results concerning the possible mechanisms implicated in the benefits of neprilisin inhibition in heart failure. It also shows for the first time in this experimental model, a protective effect on the size of acute myocardial infarction. Achieving infarct size reduction may be vital in the natural progression of ischemic heart disease, and hence, in the patient’s prognosis, enhancing the importance of these findings. Nevertheless, there are many aspects that need to be studied regarding the mechanisms leading to these marked beneficial effects; for example, the reduction of the infarct scar is noteworthy when the treatment starts at six weeks of evolution and this has no remnant viable myocardial tissue.