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Does sacubitril/valsartan work in acute myocardial infarction? The PARADISE-AMI study

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Patients with acute myocardial infarction (AMI) complicated by left ventricular dysfunction have an increased risk of death and heart failure. Numerous clinical studies have demonstrated the ability of ACE inhibitors in optimizing the outcome in this particular clinical setting. In recent years, the sacubitril/valsartan association has drastically improved the prognosis of patients with heart failure with reduced ejection fraction with a significant decrease in mortality from cardiovascular causes and hospitalizations due to acute heart failure. However, it has not yet been fully clarified whether this pharmacological association may play a role in patients with AMI. Pre-clinical studies have suggested the possibility that sacubitril/valsartan can reduce the size of the infarct scar and prevent the onset of ventricular arrhythmias in laboratory animals in which myocardial infarction was induced. On the other hand, small clinical experiences with patients after myocardial infarction have provided conflicting data. The results of the PARADISE-MI study were recently presented, which enrolled 5661 patients with AMI complicated by pulmonary congestion and left ventricular dysfunction randomized to therapy with ramipril or sacubitril/valsartan and followed up for ~2 years. Although combination therapy was associated with an ~10% reduction in the risk of death from cardiovascular causes or an episode of heart failure, this was not enough to achieve statistical significance. However, treatment with sacubitril/valsartan was shown to be more effective than ramipril in preventing recurrence of heart failure after the first one.

Introduction

Patients with acute myocardial infarction (AMI) complicated by pulmonary congestion and/or decreased left ventricular systolic function have an increased risk of mortality and chronic heart failure. Some clinical studies, which have now entered the history of cardiology, have shown how the very early use of drugs belonging to the class of ACE inhibitors is able to improve the prognosis of these patients. In the SAVE trial, for example, captopril treatment was associated with improved survival and a reduction in major adverse cardiac events (MACE) in patients with recent AMI and asymptomatic left ventricular dysfunction.¹ In the AIRE study, on the other hand, the timely

initiation of ramipril therapy significantly reduced early mortality from all causes in over 2000 patients with AMI complicated by heart failure.²

With the subsequent introduction of angiotensin receptor inhibitors (sartans), it was hypothesized that a more selective blockade of the renin-angiotensin aldosterone system could result in an even greater benefit than that observed with ACE inhibitors. This hypothesis has been tested, but not confirmed, in two large randomized clinical trials comparing ACE inhibitors and sartans in patients with recent AMI and additional risk factors. While in the OPTIMAAL study the treatment with captopril won the comparison with losartan,³ in the VALIANT the use of valsartan demonstrated an efficacy comparable to that of captopril in reducing mortality from all causes.⁴

Neprylhexin is an endopeptidase that acts by degrading some vasoactive endogenous peptides such as bradykinin,

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natriuretic peptides, and adrenomedullin. Therefore, the inhibition of neprylhexin, by increasing the levels of these substances, counterbalances the neurohormonal activation responsible for vasoconstriction, sodium retention, and negative remodelling that represents the pathophysiological substrate of heart failure. Experimental studies have shown that the combined inhibition of the renin-angiotensin and neprylhexin system produces greater haemodynamic and neurohormonal effects than the inhibition of the single pathway.⁵ It is for this reason that in recent years, valsartan has been associated with sacubitril, a neprylhexin inhibitor, giving rise to the first pharmacological agent in the class of Angiotensin and Neprylhexin Receptor Inhibitors (ARNI).

Clinical evidence for the use of sacubitril/valsartan in patients with heart failure

The trial that promoted the introduction of sacubitril/valsartan in our clinical practice was the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) which randomized over 8000 patients with heart failure and ejection fraction (EF) <40% treated with enalapril or sacubitril/valsartan 'on top' of the therapies recommended by the guidelines (beta-blockers and mineralocorticoid receptor antagonists). The study was stopped early, after only 27 months of follow-up, due to the incredible benefit shown by the patients undergoing combination therapy. At study closure, the primary endpoint, a composite of cardiovascular death and heart failure hospitalizations, occurred in 914 subjects (21.8%) in the sacubitril/valsartan arm and 1117 subjects (26.5%) in the enalapril arm [hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.73-0.87; $P < 0.001$]. Mortality was 17% (711 deaths) in the sacubitril/valsartan group and 19.8% (835 deaths) in the enalapril group (HR 0.84, 95% CI 0.76-0.93; $P < 0.001$); cardiovascular mortality was 13.3% and 16.5%, respectively (HR 0.80, 95% CI 0.71 to 0.89; $P < 0.001$). In addition, compared to enalapril, the combination therapy sacubitril/valsartan reduced the risk of new hospitalizations for heart failure by 21% ($P < 0.001$), with a significant reduction in symptoms and functional limitation ($P = 0.001$). Regarding safety and tolerability, patients treated with sacubitril/valsartan had a higher incidence of hypotension and angioedema, but less deterioration of renal function, cough, and hyperkalaemia than those treated with enalapril. The benefit of combination therapy manifested very early and was confirmed in all pre-specified subgroups.⁶

More recently the Comparison of Sacubitril–Valsartan vs. Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial compared sacubitril/valsartan and enalapril in heart failure patients with a reduced fraction of acute-phase ejection. Again, ARNI therapy proved to be more effective than the ACE inhibitor, with a significant reduction in NT-ProBNP levels already after the first week of treatment.⁷

The use of sacubitril/valsartan was also tested in heart failure with preserved ejection fraction in the Prospective Comparison of ARNI with ARB Global Outcomes in HF with

Preserved Ejection Fraction (PARAGON-HF) study which randomized 4822 patients with heart failure and $FE \geq 45\%$ on treatment with valsartan alone or with the sacubitril/valsartan combination. In this case, no significant differences were found in the primary composite endpoint of cardiovascular death and hospitalizations for heart failure (526 events in the sacubitril/valsartan group and 557 events in the valsartan group) ($P = 0.06$).⁸

Evidence for the utility of sacubitril/valsartan in patients with acute myocardial infarction

In light of these evidences, the use of sacubitril/valsartan has now fully entered the therapeutic armamentarium available to heart failure patients with reduced EF and is now recommended by the main international guidelines. However, it has not yet been fully clarified whether this pharmacological association may play a role in patients with AMI.

Preclinical studies have shown that the use of sacubitril/valsartan, through the inhibition of the activity of pro-inflammatory cytokines (interleukin-1 β and interleukin-6) and the degradation of the extracellular matrix by macrophages, carries out a protective action on heart rupture in wild-type mice in which myocardial infarction was induced by ligation of the anterior descending artery.⁹ Other pre-clinical experiences, always conducted on animals in which a myocardial infarction was caused, have shown the ability of combination therapy to prevent the onset of ventricular arrhythmias compared to enalapril¹⁰ and to reduce the size of the scar area compared to valsartan.¹¹

As regards human studies, Docherty *et al.* published a small multicentre and randomized study, in which 93 subjects with a recent history of AMI, $EF \leq 40\%$ assessed at an echocardiogram performed at least 3 months after the event of heart attack, without signs and symptoms of heart failure were randomized to treatment with valsartan or with sacubitril/valsartan. After a mean follow-up of 52 weeks, the combination therapy did not show a significant improvement on left ventricular remodelling compared to sartan alone: in fact, no significant differences were found between the two groups in end-diastolic volume and left ventricular EF evaluated by magnetic resonance, in the levels of NT-proBNP, of ultrasensitive troponin and in the functional capacity.¹²

The results of the SAVE-STEMI trial involving 200 patients with ST-segment elevation myocardial infarction (STEMI) randomized to treatment with sacubitril/valsartan or ramipril immediately after primary angioplasty were also recently disclosed. The primary efficacy endpoint of the study was 30-day and 6-month MACE defined as the composite of cardiovascular death, myocardial infarction, and hospitalizations for heart failure. While at 30 days the two groups did not show significant differences ($P = 0.18$), at 6 months the patients treated with sacubitril/valsartan had a better outcome with a significant decrease in MACE almost entirely due to the reduction in hospitalizations for heart failure (18% vs. 36%, OR 0.40, 95% 0.22-0.75; $P = 0.004$). Furthermore, at 6 months, the EF was

significantly higher in subjects treated with combination therapy than in those treated with ramipril ($46.8 \pm 12.5\%$ vs. $42.09 \pm 13.8\%$; $P=0.012$), with better remodelling of the left ventricle end-diastolic diameter 50.6 ± 3.9 vs. 53.2 ± 2.7 mm ($P=0.047$), end-systolic diameter 36.1 ± 3.4 vs. 39.9 ± 6.3 mm ($P=0.001$). On the other hand, no significant differences were observed in the other efficacy and safety endpoints (symptomatic hypotension, angioedema, hyperkalaemia, and worsening of renal function). The authors therefore concluded that these results are the first clear evidence to support that the early use of sacubitril/valsartan can improve the outcome of patients with STEMI, recognizing however the limitation that it was a single-centre experience conducted on a few patients which needs to be confirmed in a larger population and with a longer follow-up.¹³

The PARADISE-MI study

The Prospective ARNI vs. ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI) trial was designed to determine whether sacubitril/valsartan was superior to ramipril in improving the outcome of patients with AMI and factors of additional risk in terms of reduction of cardiovascular mortality and heart failure episodes.¹⁴

The main inclusion criterion of the study was AMI occurring in the seven days prior to randomization, associated with an ejection fraction (EF) $\leq 40\%$ and/or signs of pulmonary congestion evidenced by the use of intravenous (iv) diuretics. In addition, patients were required to have at least one of eight additional high-risk criteria: age ≥ 70 years, diabetes, history of previous myocardial infarction, atrial fibrillation, EF $<30\%$, Killip Class $\geq III$, non-reperused STEMI, and glomerular filtration rate <60 mL/min/1.73 m².

The main exclusion criteria were: the previous history of heart failure, the presence of hyperkalaemia (potassium >5.2 mmol/L), a history of angioedema or intolerance to ACE inhibitors and sartans, a glomerular filtration rate <30 mL/min/1.73 m², haemodynamic instability at randomization (defined as the use of IV diuretics or vasopressor agents within the previous 24 h).

Eligible patients were randomized 1:1 to treatment with ramipril or sacubitril/valsartan; the randomization was stratified by the type of infarction [STEMI vs. NSTEMI (Myocardial Infarction without ST-segment elevation)] and by the geographic region of belonging. Each treatment arm had three drug dosage levels (level 1-2-3), which for ramipril were 1.25 mg for two, 2.5 mg for two, and 5 mg for two; for sacubitril/valsartan they were 24/26 mg for two, 49/51 mg for two, and 97/103 mg for two.

The primary endpoint of the study was the composite of cardiovascular death and heart failure episodes (both necessitating hospitalization or managed in the home setting). The first of the secondary endpoints was the composite of cardiovascular death and hospitalizations for heart failure. The following were considered as additional secondary endpoints: the time to the occurrence of the

first episode of heart failure, the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, the cumulative number of single events including all hospitalizations for heart failure (both first event and recurrences).¹⁴

The trial results were previewed during the 70th edition of the American College of Cardiology Congress last May and we are awaiting their final publication. Between December 2016 and March 2020, 5661 patients were randomized into the two treatment groups (2830 sacubitril/valsartan and 2831 ramipril) which were comparable for the main clinical characteristics. The population presented an average age of 64, with about 75% of men. Randomization occurred on average at 4.3 ± 1.8 days from the index heart attack. As regards the type of heart attack, in 76% of subjects it was a NSTEMI and in 24% a STEMI which in about 11% of cases was not subjected to a reperfusion strategy; the prevailing localization was the anterior one (68%). In about 54% of the population, eligibility was due to the presence of pulmonary congestion (regardless of the EF), however, 82.6% of the subjects presented an EF $\leq 40\%$ and the mean EF was 36%. Regarding the criteria of increased risk: 47.6% of patients showed at least one factor, 30.8% two and 21.7% three or more; diabetes was the most prevalent risk criterion (42.3%). More than half of the patients had a Killip Class $\geq II$ (56%), atrial fibrillation was instead present in 13.5% of cases.

During the observation period of ~ 2 years, there were 373 events in the ramipril group and 338 events in the sacubitril/valsartan group, therefore although the combination therapy was associated with a risk reduction of approximately 10% this was not enough to reach statistical significance [HR 0.90 (0.78-1.04), $P=0.17$]. There were no significant differences between the two groups even with regard to cardiovascular deaths [sacubitril/valsartan 5.9% vs. ramipril 6.7%; HR 0.87 (0.71-1.08), $P=0.20$] and new hospitalizations for heart failure [sacubitril/valsartan 6.0% vs. ramipril 6.9%; HR 0.87 (0.70-1.06), $P=0.17$]. On the other hand, an almost significant reduction in heart failure relapses managed not in a hospital setting was observed and defined as the presence of signs and symptoms of heart failure treated with the implementation of diuretic therapy maintained for at least 28 days: the sacubitril/valsartan group presented 39 events (1.4%) vs. 57 (2.0%) of the ramipril group [HR 0.68 (0.45-1.03), $P=0.07$].

Regarding secondary endpoints, there were no significant differences in all-cause mortality, cardiovascular mortality, the incidence of new heart attacks and new strokes; however, sacubitril/valsartan was significantly more effective than ramipril in reducing the composite endpoint of cardiovascular death and total episodes (hospital, out-of-hospital, first event, recurrences) of heart failure [sacubitril/valsartan 8.4% vs. ramipril 10.1%; HR 0.79 (0.65-1.97), $P=0.02$]. The latter result was almost entirely due to the significant reduction in heart failure episodes and in particular recurrences (sacubitril/valsartan 452 events vs. ramipril 539 events; $P=0.02$).

The incidence of adverse events was very low and comparable between the two groups, with no difference regarding the occurrence of angioedema, hyperkalaemia,

renal, or hepatic insufficiency. Patients treated with sacubitril/valsartan showed a significantly higher incidence of hypotension (28.4% vs. 22%), while those treated with ramipril cough (13.1% vs. 9.0%).¹⁵

The authors of the trial therefore concluded that sacubitril/valsartan proved to be a safe and well-tolerated drug even in the population of patients with AMI complicated by heart failure; although the primary endpoint has not been reached, combination therapy has some benefits compared to ramipril, especially as regards its effectiveness in preventing relapses of heart failure after the first episode. Certainly, further analyses are needed, and we are awaiting the publication of the main trial and its sub-studies to reach more definitive conclusions and to understand if there are any subgroups of patients who could benefit from the early introduction of sacubitril/valsartan therapy in this particular clinical setting.

Conflict of interest: none declared.

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