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Valsartan/Sacubitril in heart failure and hypotension: how, when and why

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The PARADIGM-HF study demonstrated the efficacy of angiotensin receptor neprilysin inhibitor in patients with chronic heart failure secondary to left ventricular systolic dysfunction, and the new compound LCZ696 has been included in the 2016 European Society of Cardiology Guidelines. The drug has, potentially, a hypotensive action, and its introduction in clinical practice will require, akin to other important drugs such as β-blockers, particular attention. The vast majority of the patients participating the trial developed hypotension during the run-in period of Sacubitril–Valsartan treatment and were included in the randomization process, and in that phase there was no difference between Sacubitril–Valsartan group and enalapril group in the fraction of patients necessitating suspension of the drug for hypotension.

The TITRATION study[1] had the goal to test the tolerability of Sacubitril/Valsartan in a population resembling the daily clinical practice, thus including patients not previously on treatment, or with variable pre-treatment with ACEI/ARBs, following a 'condensed' or 'conservative' regimen. The primary objective of the study was to define the tolerability of the drugs as far as predefined adverse events and laboratory measures, the secondary objective to determine the proportion of patients reaching therapeutic success.

The inclusion criteria, which could be extended to the daily clinical practice, were

(1) proven previous intolerance to recommended doses of ACEI/ARBs,
(2) symptomatic hypotension,
(3) systolic blood pressure $<$100 mmHg or $>$180 mmHg at the time of recruitment,
(4) estimated glomerular filtration rate $<$30 mL/min 1.73 m^2 at the time of recruitment,
(5) history of angioedema, and
(6) hospitalization for causes other than heart failure.

After 5 days of *run-in* with Sacubitril/Valsartan 50 mg, patient were randomized in two blinded arms: (i) up-titration 'condensed' which included the up-titration of sacubitril/valsartan from 50 mg b.i.d. to 200 mg b.i.d. in 3 weeks including the *run-in* phase; (ii) a 'conservative' arm in which the titration from 50 mg b.i.d. to 200 mg b.i.d. would take 6 weeks including the *run-in* phase.

The overall rate of treatment success was 76.2% for patients passing the *run-in* phase. Treatment success was achieved by 77.8% of the patients in the up-titration 'condensed' arm, and in 84.3% of the 'conservative' arm ($P = 0.078$). Hypotension and hypokalaemia were the most common adverse events recorded but most often not severe enough as to require treatment interruption. There were two instances of angioedema but without airway involvement. The tolerability profile of the drug in the TITRATION trial was similar to the other compounds tested in the historic trial on heart failure, also when the up-titration would take 3 weeks. Accordingly, the tolerability of the drug should be considered acceptable regardless the up-titration schedule, even though patients not on previous treatment or on low doses of ACEI/ARB can reach and maintain target doses of Sacubitril/Valsartan when the titration is more gradual.

This difference was secondary to a lower incidence of hypotension, hyperkalaemia, and renal dysfunction. Patients who received higher doses of ACEI/ARB reached and maintained the target dose at 12 weeks regardless the duration of the titration schedule. In patients initially intolerant to the Sacubitril/Valsartan dose, a down-titration could be useful, allowing, eventually, to reach the target dose. The clinical implication of this study, thus, suggests a practical approach to reach the suggested Sacubitril/

Valsartan dose indicated in the trial. In a large portion of patients with heart failure and decreased systolic function, Sacubitril/Valsartan can be added to other drugs decreasing blood pressure such as beta-blockers and ACE-inhibitors, as well as aldosterone receptor blockers. A titration implemented slowly and an accurate follow-up could make the drug tolerable also for the more 'frail' patients, allowing them to reach the expected benefit of the treatment.

Conflict of interest: none declared.

Reference

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