



LETTER TO THE EDITOR

Sacubitril/valsartan: A practical guide revisited



Sacubitril/valsartan: um guia prático revisitado

To the Editor,

Since the publication in the May 2019 issue of our paper “Sacubitril/valsartan: a practical guide”,¹ which was based on the PARADIGM-HF² trial results, new evidence has become available with recent data from the TRANSITION and PIONEER-HF trials.^{3,4} On the basis of this new evidence, as the authors of the original practical guide we would like to add new considerations to our previous recommendations on the use of this drug.

Although it represents a worsening of prognosis in heart failure with reduced ejection fraction (HFrEF), hospitalization for acute heart failure constitutes an opportunity to initiate and successfully up-titrate guideline-recommended therapies. The international guidelines support the initiation and up-titration of all disease-modifying therapy (DMT) early after hemodynamic stabilization following an acute heart failure event in order to improve prognosis, particularly during the vulnerable phase early after discharge.⁵ Although this has been demonstrated for previous classes of heart failure DMT, there was still a gap in evidence on the optimal time for the initiation of sacubitril/valsartan in HFrEF patients after an acute decompensation.

The TRANSITION and PIONEER-HF trials evaluated the initiation of sacubitril/valsartan in severe HFrEF patients after stabilization following an acute heart failure episode, both before and early after discharge, with no run-in phase, closer to the challenges of everyday clinical practice.

The TRANSITION study assessed the safety and tolerability of sacubitril/valsartan in patients admitted with HFrEF, after stabilization following an acute heart failure episode. Patients were enrolled to initiate sacubitril/valsartan either in the hospital or shortly after discharge.⁶ At 10 weeks, when more than 86% of patients had been receiving sacubitril/valsartan for two weeks or longer without interruption, about half the patients in the study had achieved the primary endpoint, which was a target dose of 200 mg of sacubitril/valsartan twice daily within 10 weeks in both groups.⁵ The incidence of adverse events and discontinuation of sacubitril/valsartan due to adverse events was also similar in

both in-hospital and outpatient settings.³ The tolerability of sacubitril/valsartan in TRANSITION appears to be comparable to that reported for beta-blockers and ACEIs/ARBs under real-life conditions.^{3,7}

PIONEER-HF was designed to assess the safety, tolerability and efficacy of in-hospital initiation of sacubitril/valsartan compared to enalapril in stabilized HFrEF patients who had been admitted for acute decompensation.⁸ The primary endpoint was the time-averaged proportional change in NT-proBNP from baseline through weeks 4 and 8.^{4,8} Patients treated with sacubitril/valsartan achieved a 47% reduction from baseline in time-averaged NT-proBNP, compared to a 25% reduction with enalapril, translating into a statistically significant 29% greater reduction with sacubitril/valsartan over the ACEI (95% CI: 0.63-0.81; $p < 0.0001$).⁴ Significant reductions in NT-proBNP were observed in sacubitril/valsartan patients as early as one week after treatment initiation.⁴ There were no new safety signals identified, and the safety profile was comparable to that observed in PARADIGM-HF.^{2,4} Rates of serious adverse events occurring with a frequency of $\geq 0.5\%$ were similar between the sacubitril/valsartan and enalapril groups.⁴

In a pre-specified exploratory analysis, the composite endpoint of death, rehospitalization for HF, left ventricular assist device implantation or listing for cardiac transplant occurred in 41 (9.3%) patients in the sacubitril/valsartan group and in 74 (16.8%) in the enalapril group (HR 0.54, 95% CI 0.37-0.79; $p = 0.001$).⁴ The benefit was driven by reductions in death and rehospitalization among patients treated with sacubitril/valsartan. The number needed to treat to prevent one such clinical event during eight weeks of follow-up was 13.⁴

Moreover, TRANSITION and PIONEER-HF are the first randomized studies to provide data on the use of sacubitril/valsartan in new-onset and ACEI/ARB-naïve HFrEF patients. In fact, approximately 34% of patients in PIONEER and 29% in TRANSITION were newly diagnosed, with no prior history of heart failure, and slightly more than 50% of patients in PIONEER and 24% in TRANSITION were not receiving ACEI/ARB therapy at the time of admission.^{3,4} Recently presented data from PIONEER-HF also showed that sacubitril/valsartan, titrated to target dose based on systolic blood pressure during hospitalization, had the same beneficial effect on the primary and safety endpoints in ACEI/ARB-naïve patients.⁹

In summary, the TRANSITION and PIONEER-HF results provide complementary data to PARADIGM-HF, addressing

Table 1 Suggested revision of Table 1 in Sacubitril/valsartan: a practical guide.¹

IN WHOM AND WHEN?

Indications:

- Adult patients with heart failure and reduced ejection fraction (LVEF <40%)
- Replacement of ACEI/ARB in outpatients who remain in NYHA class II-IV despite treatment with an ACEI/ARB, a beta-blocker and an MRA
- Before discharge, in stabilized patients admitted with a primary diagnosis of decompensated or de novo acute heart failure, irrespective of prior ACEI/ARB exposure
- Patients should have SBP \geq 100 mmHg and serum potassium level <5.5 mmol/L.

previous gaps in evidence. They support the use of sacubitril/valsartan both during hospital stay and in outpatient settings. Although there are still a few unanswered questions and unpublished results from both trials, the data from PIONEER-HF and TRANSITION support the in-hospital initiation of sacubitril/valsartan in all NYHA II-III patients early after stabilization, and independently of prior HF diagnosis or ACEI/ARB exposure. There are now grounds for initiating therapy in HFrEF with ACEI safely as a first option, in both in-hospital and outpatient settings.

On the basis of this new information, our paper "Sacubitril/valsartan: a practical guide" should be revisited as in Table 1.

Conflicts of interest

Cândida Fonseca has received fees from Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Novartis, Orion, Roche, Servier and Vifor (companies that develop and market tests and/or treatments in the area of HF) for HF consulting, sitting on clinical study steering committees and giving lectures at congresses and other scientific sessions. Dulce Brito has received fees from Novartis, Orion, Roche, Servier, St. Jude and Vifor (companies that develop and market tests and/or treatments in the area of HF) for HF consulting, and has given talks at congresses and other scientific sessions. She also reports consultancy and research fellowships from Genzyme-Sanofi and consultancy and lecture fees from Pfizer, and has attended meetings sponsored by Shire Human Genetic Therapies (companies that develop and market treatments in the area of cardiomyopathies). Jorge Ferreira has received consulting and speaker fees from Amgen, AstraZeneca, Boehringer-Ingelheim, Merck-Sharp & Dohme, Novartis, and Orion. Fátima Franco has received consulting and speaker fees from Novartis. João Morais received honoraria within the last two years from pharmaceutical companies for consulting activities (Bayer Healthcare, Astra Zeneca, Merck Sharp & Dhome, Novartis) and fees for lectures (Boehringer Ingelheim, Bial, Servier, Daiichi Sankyo, Boston Scientific). He is also National Coordinator for the PARADISE-MI trial on sacubitril/valsartan in patients with myocardial infarction. José Silva Cardoso was

national coordinator of the PARADIGM-HF study and was a consultant for Novartis, AstraZeneca Pharmaceuticals, Orion, Pfizer, Servier and Vifor (companies that develop and market treatments for HF). He has sat on steering committees for clinical studies sponsored by Novartis, Orion and Pfizer and has received honoraria as a speaker in sessions on HF and research fellowships from Novartis, Abbott, AstraZeneca Pharmaceuticals, Bial, Boehringer Ingelheim, Menarini, Merck Serono, Merck Sharp & Dohme, Orion, Pfizer, Sanofi, Servier and Vifor.

References

1. Fonseca C, Brito D, Ferreira J, et al. Sacubitril/valsartan: a practical guide. *Rev Port Cardiol.* 2019;38(5):309–13.
2. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004.
3. Wachter R, Senni M, Belohlavek J, et al. P886 Initiation of sacubitril/valsartan in hospitalized patients with heart failure with reduced ejection fraction after hemodynamic stabilization: primary results of the TRANSITION study. *Eur Heart J.* 2018;39 Suppl. 1, ehy564.P886.
4. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med.* 2019;380(6):539–48.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37:2129–200.
6. Pascual-Figal D, Wachter R, Senni M, et al. Rationale and design of TRANSITION: a randomized trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan. *ESC Heart Fail.* 2018;5:327–36.
7. Maggioni AP, Anker SD, Dahlstrom U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2013;15:1173–84.
8. Velazquez EJ, Morrow DA, DeVore AD, et al. Rationale and design of the comParlson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode (PIONEER-HF) trial. *Am Heart J.* 2018;198:145–51.
9. Ambrosy AP, DeVore A, Morrow D, et al. Prior exposure to a conventional renin-angiotensin system antagonist and angiotensin receptor-neprilysin inhibition in acute decompensated heart failure: a prespecified subgroup analysis of the PIONEER-HF trial. In: Presented at ACC19 (American College of Cardiology annual meeting). 2019.

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