Titration process and predictors of achieving target dose of sacubitril/valsartan in patients with chronic heart failure and reduced ejection fraction attending to an outpatient heart failure clinic.

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Topic(s):
Chronic Heart Failure: Pharmacotherapy

Citation:
Background
Data from recent clinical trials indicate that sacubitril/valsartan can be successfully initiated and uptitrated to the maximum target dose in most patients with stable chronic heart failure. However, there is relatively little information about the titration process in real-world heart failure patients.

Purpose
To assess the characteristics and clinical outcome of unselected patients with stable chronic heart failure during the titration period of sacubitril/valsartan and to identify predictors of achieving maximum target dose.

Methods
We collected data from 64 consecutive patients attending to our outpatient heart failure clinic who started sacubitril/valsartan between May 2018 and November 2018. Patients were uptitrated based on the attending physician judgment with the goal of achieving sacubitril/valsartan 200 mg twice daily. Variables were collected baseline and at the end of the titration period.

Results
At baseline, mean age was 63±10 and 76,6% men. Mean LVEF 28±6%. 39% had ischemic etiology. Mean NYHA class 2,3±0,4. Median NT-proBNP level 1176 pg/ml (IQR 364-3945), mean glomerular filtration rate (GFR CKD-EPI) 71,7±20,6 mL/min, serum potassium 4,4±0,4 mEq/L. 84% of patients received ACE inhibitors (median enalapril equivalent dose 7,5 mg/day, IQR 5-13.7) or angiotensin receptor blockers (median equivalent valsartan dose 80 mg/day, IQR 60-160). 95% received beta-blockers and 86% mineralocorticoid receptor antagonists (MRA). The median time between starting medication and the end of the titration (titration period) was 6,5 weeks (IQR 3-13,2). 10 patients (15.6%) discontinued therapy due to adverse events. Among patients tolerating therapy, 23 (42,6%) achieved the maximum target dose. At the end of the titration period 18 patients (33,3%) improved at least one stage in NYHA class. A reduction in furosemide equivalent dose (52,3±39,2 mg vs 45,5±41,4 mg, p=0.005) was observed. Before starting sacubitril/valsartan, lower systolic blood pressure (SBP), lower GFR CKD-EPI and previous treatment with MRA were associated with not achieving maximum target dose (all p<0.05). In a multivariate analysis adjusted by age, GFR CKD-EPI, SBP, kalaeamia and previous treatment with MRA, a lower GFR CKD-EPI before starting titration (OR 0,95 95% CI 0,91-0,99 p=0.01) and previous treatment with MRA (OR 16,4 95% CI 1,6-164 p=0.01) were independently associated with not achieving maximum target dose.

Conclusions
In this cohort of unselected patients with stable chronic heart failure, the proportion who achieved maximum target dose of sacubitril/valsartan was lower than the reported in controlled clinical trials, despite a longer titration time. However, clinical benefit was observed at the end of the titration period. The difficulty to achieve maximum doses in patients treated with MRA could suggest a subgroup with a higher degree of neurohormonal blockade, needing a more careful adjustment of concomitant treatment, mainly diuretics and vasodilators.
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