Cardiovascular Topics

Usefulness of a titration algorithm for de novo users of sacubitril/valsartan in a tertiary centre heart failure clinic

Émilie Laflamme, Audrey Vachon, Sylvain Gilbert, Julie Boisvert, Vincent Leclerc, Mathieu Bernier, Pierre Voisine, Mario Sénéchal, Sébastien Bergeron

Abstract

Background: A reduction in the rate of death and hospitalisations in patients with heart failure (HF) with reduced ejection fraction receiving sacubitril/valsartan compared to enalapril was demonstrated in the PARADIGM-HF study. However, tolerability when initiating and optimising sacubitril/valsartan treatment in real clinical practice is unknown.

Methods: We performed a prospective cohort study of clinical and biochemical parameters of the first 100 patients receiving sacubitril/valsartan in a tertiary HF clinic. Patients had titration of the molecule guided by an algorithm developed by pharmacists and cardiologists in the clinic. The objective was to evaluate the proportion of patients reaching the maximal dosage, the time to reach maximal dosage, and the rate of adverse events, as well as the required modification of other HF therapy during the sacubitril/valsartan titration.

Results: Forty-six per cent of patients reached the sacubitril/valsartan maximal dose of 97/103 mg (200 mg) twice daily and 73% received at least 49/51 mg (100 mg) twice daily. Mean titration time was $30 \pm 9$ days. Symptomatic hypotension, renal dysfunction (increase in creatinine level > 30%) and hyperkalaemia (potassium level > 5.5 mmol/l) occurred in nine, four and 2% of patients, respectively. Background HF pharmacological treatment remained stable during the sacubitril/valsartan titration but daily dosage of furosemide was reduced by 13% ($p = 0.0005$).

Conclusions: This algorithm is a safe and easy-to-use tool in daily clinical practice for the introduction and titration of sacubitril/valsartan. Almost half of the patients reached the maximal dose, with a tolerability profile in line with the original study.

Keywords: heart failure, sacubitril/valsartan, algorithm, titration

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Heart failure (HF) is one of the most significant healthcare issues in contemporary medicine. More than a million Canadians are affected by heart disease and 600 000 are suffering from HF.1 Angiotensin converting enzyme inhibitors (ACEI) were the first treatment that demonstrated a reduction in the rate of death, hospitalisations and symptoms in HF in patients with reduced ejection fraction (HFrEF).2,3 Similar benefits were later found with beta-blockers4,5 and with mineralocorticoid receptor antagonists (MRA), in addition to ACEI.6,7 This triple therapy is nowadays the standard of care for patients with HFrEF. More than a decade has passed without any significant pharmaceutical therapeutic innovation besides device implantation for cardiac resynchronisation therapy8-11 and cardioverter–defibrillator implantation.12,13

Recently, a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker (ARB), was compared to enalapril in the PARADIGM-HF study.14 In this trial, the investigators demonstrated an absolute risk reduction of 4.7% for cardiovascular mortality or first hospitalisation for HF in patients treated with sacubitril/valsartan compared to enalapril. Despite hypotension occurring in 14% of the patients, this new drug proved to be safe. In response to those important results, Canadian guidelines now recommend changing ACEI or ARB for sacubitril/valsartan in patients who remain in New York Heart Association (NYHA) class II–III despite maximal therapy with ACEI or ARB, beta-blockers and MRAs.15

The purpose of this study was to present real-life clinical experience and tolerability of sacubitril/valsartan. We describe the first 100 patients treated with this new drug, titrated according to an algorithm developed in a tertiary centre HF clinic.

Methods

A prospective evaluation of the HFrEF patients who were started on sacubitril/valsartan therapy was conducted at the Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ). Inspired by the PARADIGM-HF and TITRATION trials, a committee of nine cardiologists and five pharmacists developed an algorithm to guide initiation and over-the-phone
titration of sacubitril/valsartan (Fig. 1). The first 100 patients in whom sacubitril/valsartan was initiated were included in this analysis.

The decision to initiate the drug was left to the treating cardiologist, but patients had to meet the following criteria: HFrEF [left ventricular ejection fraction (LVEF) ≤ 40%], systolic blood pressure of 100 mmHg or more, NYHA class II–III, potassium level less than 5.4 mmol/l while being on an ACEI or ARB, and glomerular filtration rate of more than 30 ml/min/1.73m². Patients who did not meet those criteria and those with a previous history of angioedema, renal replacement therapy, orthostatic hypotension and fall secondary to hypotension were not approached to initiate sacubitril/valsartan treatment.

**Fig. 1.** Titration algorithm. ACEI: angiotensin converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin receptor blocker; BID: twice daily; BP: blood pressure; BUN: blood urea nitrogen; CCB: calcium channel blocker; Creat: creatinine level; K+: potassium level; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RAAS: renin–angiotensin–aldosterone system; SBP: systolic blood pressure.
When patients were already treated with an ARB, sacubitril/valsartan was started the day after the cessation of the ARB. Patients receiving an ACEI waited 36 to 48 hours after their last dose before starting sacubitril/valsartan, ensuring a proper wash-out period, to avoid angioedema. The product monograph recommends 36 hours for the wash-out period but it was extended to 48 hours in this study for patients on once-daily ACEI to facilitate adherence. According to the algorithm, titration was subsequently based on ACEI or ARB doses and baseline systolic blood pressure.

This prospective study was done with the agreement of IUCPQ directors, and patients were informed at the beginning of the treatment that their evolution under this new medication would be screened for evaluation for the medical quality act. An informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

The objective of this study was to evaluate the usefulness of a titration algorithm in patients naïve to sacubitril/valsartan. The benefits of sacubitril/valsartan were clearly demonstrated in the PARADIGM-HF study, but safety and ease of use still had to be demonstrated in real-life practice.

The primary outcome was the proportion of patients able to tolerate the maximal dose of 97/103 mg (200 mg) twice daily. The secondary outcomes included the time needed to get to the final titration, which corresponds to the maximal tolerated dose for each patient, the variation of blood pressure from baseline values, the incidence of symptomatic hypotension (defined as any lowering in systolic blood pressure with related symptoms), the incidence of hyperkalaemia (serum potassium increase to > 5.5 mmol/l), the incidence of acute renal failure (30% increase in creatinine level from baseline or more), variation of the baseline systolic blood pressure.

The sacubitril/valsartan maximal dose of 97/103 mg (200 mg) twice daily was reached in 46% of patients and 73% had a dose ≥ 130 μmol/l in 21% of the cohort. Baseline ACEI/ARB dose was ≥ 50% of the target dose recommended by practice guidelines in 41% of the patients.

Systolic blood pressure at baseline was ≤ 110 mmHg in 25% of patients and 35% had LVEF ≤ 20%. Baseline creatinine was ≥ 130 μmol/l in 21% of the cohort. Baseline ACEI/ARB dose was ≥ 50% of the target dose recommended by practice guidelines in 41% of the patients.

The sacubitril/valsartan maximal dose of 97/103 mg (200 mg) twice daily was reached in 46% of patients and 73% had a dose ≥ 49/51 mg (100 mg) twice daily at the final titration. The mean final daily dose was 285 ± 125 mg for a median value of 350 mg. Sacubitril/valsartan dosage at the end of titration is reported in Fig. 2.

Among the treated patients who tolerated up-titration (88 patients), 42 (47%) did not attain the maximal dose of 97/103 mg twice a day. The most frequent reason for submaximal titration was low blood pressure (25 patients). Titration was also limited by orthostatic hypotension (three patients), dizziness (four patients), fatigue (one patient), upper-limit potassium level (two patients), fatigue (one patient), upper-limit potassium level (two patients), and the need for downtime or discontinuation of sacubitril/valsartan.

### Statistical analysis

Data are expressed using mean ± standard deviation for continuous variables or as a percentage for categorical data. First and last measurements were analysed using a mixed model as appropriate; the normality assumption was verified with the Shapiro–Wilks tests on the error distribution from the Cholesky factorisation. The results were considered significant with p-values ≤ 0.05. All analyses were conducted using the statistical package SAS v 9.4 (SAS Institute Inc, Cary, NC, USA).

### Results

From December 2015 to August 2016, 100 patients in whom sacubitril/valsartan was initiated were titrated to the maximal tolerated dose. Table 1 shows demographic and clinical baseline characteristics of the patients. The majority of patients were men with NYHA functional class II who had HF of ischaemic aetiology. They were all on optimal tolerated medical therapy and the mean systolic blood pressure was ± 16 mmHg. Twenty-seven per cent of the patients were ≥ 70 years old and 5% were ≥ 80 years old.

Systolic blood pressure at baseline was ≤ 110 mmHg in 25% of patients and 35% had LVEF ≤ 20%. Baseline creatinine was ≥ 130 μmol/l in 21% of the cohort. Baseline ACEI/ARB dose was ≥ 50% of the target dose recommended by practice guidelines in 41% of the patients.

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>76</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy (%)</td>
<td>56</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>26 ± 7</td>
</tr>
<tr>
<td>Mean creatinine level (μmol/l)</td>
<td>104 ± 29</td>
</tr>
<tr>
<td>Mean systolic blood pressure (mmHg)</td>
<td>122 ± 16</td>
</tr>
<tr>
<td>Functional class</td>
<td></td>
</tr>
<tr>
<td>NYHA I (%)</td>
<td>1</td>
</tr>
<tr>
<td>NYHA II (%)</td>
<td>73</td>
</tr>
<tr>
<td>NYHA III (%)</td>
<td>26</td>
</tr>
<tr>
<td>NYHA IV (%)</td>
<td>0</td>
</tr>
<tr>
<td>ICD (%)</td>
<td>70</td>
</tr>
<tr>
<td>CRT (%)</td>
<td>40</td>
</tr>
<tr>
<td>Medical treatment</td>
<td></td>
</tr>
<tr>
<td>ACEI (%)</td>
<td>71</td>
</tr>
<tr>
<td>ARB (%)</td>
<td>29</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>98</td>
</tr>
<tr>
<td>MRA (%)</td>
<td>71</td>
</tr>
<tr>
<td>Loop diuretic (%)</td>
<td>80</td>
</tr>
</tbody>
</table>

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CRT: cardiac resynchronisation therapy; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association.

![Fig. 2. Sacubitril/valsartan maximal tolerated dose at end of titration.](#)
patients), ongoing diuretic titration (one patient), hospitalisation for aortic and mitral valve replacement (one patient), lack of adherence to the follow up (three patients), heart transplant (one patient) and sulfasalazine-related hepatitis (one patient).

Mean titration time (drug initiation to maximal tolerated dose) was 30 ± 9 days. At the end of titration, mean systolic blood pressure was 110 ± 16 mmHg, which represents a reduction of 12 mmHg (9.8%) when compared to the baseline value (p < 0.0001).

Modification of baseline HF therapy during the on-treatment phase was also recorded (Table 2). The mean daily dose of loop diuretic significantly decreased during follow up (13% reduction, p = 0.0005). Beta-blocker and MRA dosages remained similar during titration of sacubitril/valsartan.

Symptomatic hypotension, renal dysfunction and hyperkalaemia occurred in nine (9%), four (4%) and two patients (2%), respectively. Sacubitril/valsartan down-titration occurred in eight patients (8%), and six (6%) had to stop the medication. Among the causes of discontinuation, one patient underwent heart transplant and one had hepatitis related to sulfasalazine. Sacubitril/valsartan was resumed after the patient recovered from liver injury.

Sacubitril/valsartan was also stopped in two cases for acute renal failure (associated with hypotension in one patient), one for symptomatic hypotension and one for dizziness. Among the patients with symptomatic hypotension, five required sacubitril/valsartan dose reduction. The sacubitril/valsartan dose was also decreased in two cases of acute renal failure and one case of hyperkalaemia.

**Discussion**

Regarding the primary outcome, the maximal target dose was reached in 46% of patients. Furthermore, 73% of patients had a final dose of at least 49/51 mg (100 mg) twice daily. The PARADIGM-HF study included two single-blind run-in periods before randomisation, during which patients had to tolerate both enalapril and sacubitril/valsartan target doses. Around 20% of patients were excluded after this phase and there is therefore a possibility that patients selected for the PARADIGM-HF cohort may differ from the real-world, all-comer population of HF clinics in 2017, limiting the applicability of its findings outside research protocols.

In the cohort presented here, 41% of patients had a baseline ACEI/ARB dose that was inferior or equal to 50% of the target dose recommended by practice guidelines because of tolerability issues (blood pressure, dizziness, renal function) or ongoing titration. These results are quite similar to what has already been reported in many real-life cohorts. In fact, a prospective, observational trial by Maggioni et al. demonstrated that around 92% of HFrEF patients were appropriately treated with an ACEI/ARB but only 29% were at target doses.

Another retrospective cohort from Lenzen et al. showed that among 10,701 patients included in the Euro Heart Survey on Heart Failure, only 9% would have met inclusion criteria to be randomised in the SOLVD trial (Study Of Left Ventricular Dysfunction). Furthermore, even among eligible SOLVD patients of that real-life cohort, only 41% were actually receiving target doses of ACEI, as recommended by guidelines.

These real-life studies clearly show the existing gap between clinical trials and implementation in daily practice. This reality described with ACEI could certainly be transposed to sacubitril/valsartan. In our cohort, a significant proportion of patients did not receive ACEI/ARB target doses at baseline and less than 50% of the patients finally reached the maximal dose of the angiotensin receptor neprilysin inhibitor (ARNI), which is in accordance with previous real-life trials of HF treatment.

In a recent post hoc analysis from PARADIGM-HF, Vardeny et al. demonstrated that the need for sacubitril/valsartan dose reduction during follow up identifies patients with higher cardiovascular risk. Their findings suggested that patients with lower doses still benefited from sacubitril/valsartan compared to lower doses of enalapril. We therefore believe that most of our patients benefit from titration to the maximal tolerated dose of sacubitril/valsartan, even if they do not reach the maximal recommended dose.

The most important secondary outcome of this prospective study was the safety of sacubitril/valsartan. The incidence of hypotension and hyperkalaemia in our cohort was lower than in the original trial. In fact, 9% of patients had symptomatic hypotension compared to 14% in PARADIGM-HF, and hyperkalaemia was less frequent (two vs 16.1%). Acute renal failure episodes were also uncommon (4%). Considering the low occurrence of adverse events, it appears that our algorithm is safe and that some patients might tolerate faster titration.

Our study is in accordance with Senni and co-workers’ findings previously published in the TITRATION trial, where a shorter titration course (three weeks) was shown to be as safe as a longer titration regimen (six weeks). However, for patients on lower baseline doses of ACEI or ARB, longer titration helped to achieve the maximal sacubitril/valsartan dose while minimising hypotension events.

Our study demonstrates that with the use of our titration algorithm for new ARNI users, the introduction of sacubitril/valsartan led to a significant reduction in furosemide dosage, possibly explained by the natriuretic effect of sacubitril/valsartan. Furthermore, neither down-titration nor discontinuation of other well-established pharmacological HF treatment occurred.

Overall, patients in our cohort are comparable with the PARADIGM-HF population. Age, systolic blood pressure, creatinine level and functional class were similar. As in the PARADIGM-HF study, most of the patients were on optimal

<table>
<thead>
<tr>
<th>Mean daily dose</th>
<th>Furosemide (n = 80)</th>
<th>Metoprolol (n = 29)</th>
<th>Bisoprolol (n = 61)</th>
<th>Carvedilol (n = 84)</th>
<th>Spironolactone (n = 59)</th>
<th>Eplerenone (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mean ± SD (median) (mg)</td>
<td>62 ± 53 (40)</td>
<td>93 ± 45 (100)</td>
<td>6.0 ± 3.3 (5)</td>
<td>45 ± 10 (50)</td>
<td>19.7 ± 11.0 (12.5)</td>
<td>30 ± 13 (25)</td>
</tr>
<tr>
<td>Final dose,* mean ± SD (median) (mg)</td>
<td>54 ± 55 (40)</td>
<td>93 ± 45 (100)</td>
<td>5.8 ± 3.3 (5)</td>
<td>45 ± 10 (50)</td>
<td>19.1 ± 11.0 (12.5)</td>
<td>28 ± 11 (25)</td>
</tr>
<tr>
<td>p-value**</td>
<td>0.0005</td>
<td>1.0</td>
<td>0.6</td>
<td>1.0</td>
<td>0.31</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Final dose is the mean daily dose of medication that was taken when the patient reached the maximal tolerated dose of sacubitril/valsartan.

**p-values were calculated with mean doses.
therapy, but a higher proportion of our patients were using MRA (71 vs 56%). Mean LVEF was slightly lower in our cohort (26 vs 30%) and patients were more frequently treated with cardiac resynchronisation therapy (40 vs 7%) and implantable cardioverter–defibrillator devices (70 vs 15%).

The study has some limitations. The purpose of this study was to safely acquire clinical experience with sacubitril/valsartan initiation and titration. Therefore, selection bias might have occurred. Death and hospitalisation rates were not analysed in this study as the number of patients and follow-up duration could not provide reliable information on these issues. Finally, NT-proBNP levels were not used as inclusion criteria because they are not part of Health Canada and United States Food and Drug Administration recommendations.

Conclusions

This prospective evaluation demonstrated that our algorithm for titration of sacubitril/valsartan, developed in a tertiary HF clinic, is a safe and easy-to-use tool in daily practice. Using this titration algorithm, we were able to reach the maximal dose of sacubitril/valsartan in almost half of our patients, with a tolerability profile in line with the original PARADIGM-HF study.

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References