



Original Article

Canadian Real-World Experience of Using Sacubitril/Valsartan in Patients With Heart Failure With Reduced Ejection Fraction: Insight From the PARASAIL Study

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ABSTRACT

Background: To determine the effectiveness of sacubitril/valsartan 97/103 mg twice daily (b.i.d.) on tolerability, safety, and quality of life (QoL) in Canadian patients with heart failure with reduced ejection fraction in a real-life setting.

Methods: In Prospective, Multicenter, Open Label, Post-Approval Study Aimed at Characterizing the Use of LCZ696 at 97 mg Sacubitril/103 mg Valsartan bid in Patients With HFrEF (PARASAIL), an open-label, prospective, phase IV, multicentre study, outpatients with heart failure with reduced ejection fraction and New York Heart Association functional class II-III were followed up for 12 months. The suggested starting dose of sacubitril/valsartan was 24/26 mg b.i.d. replacing angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, with an uptitration to 97/103 mg b.i.d. or as per clinical

RÉSUMÉ

Contexte : L'objectif était de déterminer, en contexte réel, l'efficacité de l'association sacubitril à 97 mg/valsartan à 103 mg, deux fois par jour, sous l'angle de la tolérabilité, de l'innocuité et de la qualité de vie (QV) chez des patients canadiens atteints d'insuffisance cardiaque avec fraction d'éjection réduite.

Méthodologie : Au cours de l'étude multicentrique et prospective sans insu de phase IV PARASAIL (*Prospective, Multicenter, Open Label, Post-Approval Study Aimed at Characterizing the Use of LCZ696 at 97 mg Sacubitril/103 mg Valsartan bid in Patients With HFrEF*), des patients externes atteints d'insuffisance cardiaque de classe fonctionnelle II ou III selon la NYHA (*New York Heart Association*) avec fraction d'éjection réduite ont été suivis durant 12 mois. La dose initiale recommandée était de 24 mg de sacubitril/26 mg de valsartan,

Chronic heart failure (HF) is one of the leading causes of hospitalization and mortality worldwide.¹ HF significantly impacts the exercise capacity and overall quality of life (QoL) of patients.²

Overall, HF is prevalent in 2% of adult population worldwide, and as of 2016, it affects approximately 600,000 patients in Canada with high health care resource use for HF with both reduced and preserved ejection fraction (EF).³⁻⁵ The aim of pharmacologic management of HF is to improve the disease symptoms and reduce morbidity and mortality. In patients with heart failure with reduced ejection fraction (HFrEF), sacubitril/valsartan is recommended as a replacement for angiotensin-converting enzyme inhibitors (ACEIs) to further reduce the risk of HF-related hospitalization and death in ambulatory patients who remain symptomatic, despite optimal HF treatment.^{6,7} Indeed, the Canadian guidelines for the management of HF recommend to replace ACEI or angiotensin receptor blocker (ARB) with an angiotensin receptor neprilysin inhibitor

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Ethics Statement: The study was performed according to the Declaration of Helsinki and the International Conference on Harmonisation and Good Clinical Practice guidelines. The protocol was approved by an independent organization, that is, central ethics committee and local ethics committees for all of the participating sites.

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judgement. The primary endpoint was the proportion of patients achieving the target dose of sacubitril/valsartan 97/103 mg b.i.d. after 6 months of treatment.

Results: For the 302 patients included, the mean age was 64.47 years, and a majority of patients (82.8%) belonged to New York Heart Association class II. Overall, 195 (64.6%) patients were on maximum dose of sacubitril/valsartan 97/103 mg b.i.d. after 6 months and 62.3% remained on this dose at month 12. Using patient global assessment, patients experienced an improvement in QoL. For Minnesota Living with Heart Failure Questionnaire scores, a significant decrease from the baseline was observed at weeks 4, 12, and 24 ($P < 0.0001$ for all), which indicated an improvement in QoL. The patient global assessment and Minnesota Living with Heart Failure Questionnaire results correlate with moderate but significant changes in Euro quality of life-5D visual analogue scale scores.

Conclusions: Results of the PARASAIL study in a real-life setting have shown that most patients were on sacubitril/valsartan 97/103 mg b.i.d. and the treatment was well tolerated. The patient-reported outcomes showed an overall improvement in patients' QoL.

(sacubitril/valsartan) in patients who remain symptomatic despite optimal therapy.⁸

Evidence from the prospective clinical trial, which compared angiotensin receptor neprilysin inhibitor with enalapril (ACEI) to determine the impact on global mortality and morbidity in HF (Prospective Comparison of ARNi With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF]), demonstrated that sacubitril/valsartan reduced the risk of cardiovascular death and HF-related hospitalization, and improved QoL in patients with HFrEF.⁹ It also reported an improvement in the overall health-related QoL at 8 months with sacubitril/valsartan compared with enalapril in surviving patients as determined by the Kansas City Cardiomyopathy Questionnaire.⁹ The magnitude of this improvement in the PARADIGM-HF was comparable to health-related QoL improvement observed with cardiac resynchronization therapy.¹⁰ In addition, a pilot study showed an improvement in exercise tolerance after 30 days of treatment initiation with sacubitril/valsartan using the 6-minute walk test (6-MWT) as an outcome measure.¹¹

The generalizability of results from randomized clinical trials (RCTs) to "real-world" clinical setting is limited as routine clinical practice involves a broader and larger patient population in a less controlled environment. Phase IV studies evaluate the real-world effectiveness of drugs in observational and noninterventional manner that complements the efficacy data emanating from a premarketing RCT.

The 2 previous RCTs, PARADIGM-HF and TITRATION, reported that initiation and up-titration of sacubitril/valsartan was well tolerated in patients with HFrEF.^{9,12} However, there is a need to assess the effectiveness of up-titration regimen aimed at

deux fois par jour, à la place d'un inhibiteur de l'enzyme de conversion de l'angiotensine ou d'un antagoniste des récepteurs de l'angiotensine; la dose devait être augmentée à 97 mg de sacubitril/103 mg de valsartan, deux fois par jour, ou selon le jugement du clinicien. Le critère d'évaluation principal était la proportion de patients chez qui la dose cible de 97 mg de sacubitril/103 mg de valsartan, deux fois par jour, se trouvait atteinte après six mois de traitement.

Résultats : L'âge moyen des 302 patients admis était de 64,47 ans. La majorité de ces patients (82,8 %) présentaient une insuffisance cardiaque de classe II selon la NYHA. Globalement, 195 (64,6 %) patients prenaient la dose maximale de 97 mg de sacubitril/103 mg de valsartan, deux fois par jour, après six mois de traitement; 62,3 % continuaient de prendre cette dose à 12 mois de traitement. L'évaluation globale des patients indique une amélioration de leur QV. Les scores au *Minnesota Living With Heart Failure Questionnaire* avaient significativement diminué par rapport aux scores de départ aux semaines 4, 12 et 24 ($p < 0,0001$ à tous les temps d'évaluation), ce qui indique une amélioration de la QV. L'évaluation globale des patients et les scores au *Minnesota Living With Heart Failure Questionnaire* sont corrélés avec des variations modérées, mais significatives des scores de QV à l'échelle visuelle analogique du questionnaire EQ-5D.

Conclusions : Les résultats obtenus en contexte réel au cours de l'étude PARASAIL montrent que la plupart des patients prenaient la dose de 97 mg de sacubitril/103 mg de valsartan, deux fois par jour, et que le traitement était bien toléré. Les résultats rapportés par les patients témoignent d'une amélioration globale de la QV de ces derniers.

achieving the optimal dose of sacubitril/valsartan 97/103 mg twice daily (b.i.d.) in a real-life setting. The Prospective, Multi-center, Open Label, Post-Approval Study Aimed at Characterizing the Use of LCZ696 at 97 mg Sacubitril/103 mg Valsartan bid in Patients With HFrEF (PARASAIL) study (ClinicalTrials.gov: NCT02690974) is aimed at addressing this knowledge gap by characterizing the tolerability, safety, and QoL effectiveness of sacubitril/valsartan 97/103 mg b.i.d. in Canadian patients with HFrEF in the real-life setting.

Methods

Study design

PARASAIL was a 52-week, open-label, prospective, post-approval (phase IV), multicentre study involving 32 sites across Canada (Fig. 1). The study patients were enrolled with Canadian community cardiologists and internal medicine specialists who treat patients with HFrEF. The list of participating investigators and institutions is presented in Supplemental Table S1. All eligible patients discontinued prior ACEI treatment and underwent 36-hour washout period before receiving open-label sacubitril/valsartan 24/26 mg b.i.d. as per the product monograph. Patients were up-titrated to sacubitril/valsartan 49/51 mg b.i.d. within 2-4 weeks of enrollment, and to a target dose of sacubitril/valsartan 97/103 mg b.i.d. within 2-4 weeks from first up-titration as tolerated by the patient and in accordance with the product monograph.

Patients continued with the background therapy with dose modification of nitrates, calcium channel blockers, α -blockers, β -blockers, and diuretics as per clinical judgement, except

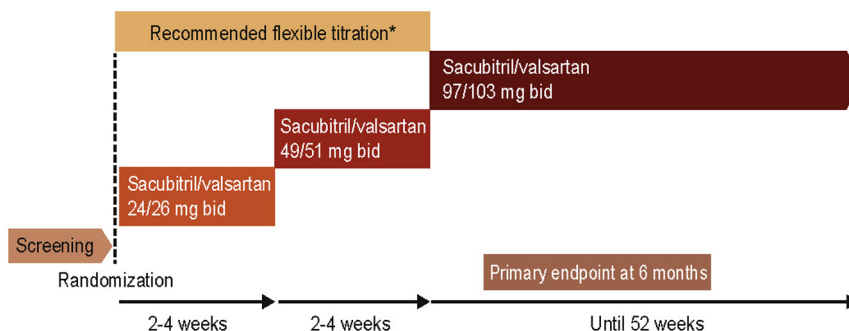


Figure 1. Prospective, Multicenter, Open Label, Post-Approval Study Aimed at Characterizing the Use of LCZ696 at 97 mg Sacubitril/103 mg Valsartan bid in Patients With HFrEF (PARASAIL) study design. *Titration scheme in the study protocol reflects the approved Canadian product monograph. bid, twice daily.

ACEI or ARB. Patients who could not tolerate the intermediate or target doses of sacubitril/valsartan were down-titrated to lower dose levels defined as per the product monograph and in response to the tolerability issues, including, but not limited to, symptomatic hypotension or hyperkalemia.

Study visits were scheduled at baseline and weeks 2, 4, 12 (month 3), 24 (month 6), and 52 (month 12). Written informed consent was provided by all patients before their enrollment. The protocol was approved by an independent organization, that is, central ethics committee (IRB Services, Aurora, Ontario, Canada) and by local ethics committee for all sites. The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Study population

Male or female outpatients (aged ≥ 18 and ≤ 80 years) with HF (New York Heart Association [NYHA] functional class II-III) and reduced left-ventricular ejection fraction ($\leq 40\%$) and eligible for treatment with sacubitril/valsartan as per the Canadian monograph were included in the study.¹³ The eligible patients treated with ACEIs or ARBs and β -blockers had to be on stable doses of these medications before enrollment. Patients were excluded if they had symptomatic hypotension and/or a systolic blood pressure < 100 mm Hg, estimated glomerular filtration rate < 30 mL/min/1.73 m² at baseline visit, a known history of angioedema related to previous ACEI or ARB therapy or a history of hereditary or idiopathic angioedema or required treatment with both ACEIs and ARBs.

Study endpoints

The primary endpoint was to evaluate the proportion of patients achieving the sacubitril/valsartan 97/103 mg b.i.d. dose after 6 months of treatment.

The secondary endpoints are provided in Table 1. The titration of sacubitril/valsartan consisted of a “swift scheme” defined as 24/26 to 49/51 to 97/103 mg in ≤ 8 weeks or 49/51 to 97/103 mg in ≤ 4 weeks. A “conservative scheme” defined as 24/26 to 49/51 to 97/103 mg in > 8 weeks and “other titration scheme” consisting of patients who did not reach 97/103 mg.

Overall safety assessments comprised monitoring of all adverse events (AEs), serious AEs, and the shift in the NYHA class.

The exploratory endpoints included patient-reported outcomes such as change in the patient global assessment (PGA),

Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores, and Euro quality of life-5D (EQ-5D) Questionnaire scores from baseline to weeks 4, 12, and 24.

Statistical analysis

The data from clinical studies have shown that at 12 weeks approximately 80% patients achieve a dose of sacubitril/valsartan 97/103 mg. In this real-world study of 12 months (primary endpoint was evaluated at 6 months), a reasonable estimate of patients achieving this dose would be 70%. A total of 302 patients were enrolled in the study, considering a 95% confidence interval (CI) of $\pm 5.2\%$, which is equivalent to 7.4% point estimate of 70% resulting in upper and lower limits of 64.8% and 75.2%, respectively.

The PARASAIL study was not driven by hypothesis as the data analysis was primarily descriptive. The descriptive statistics included mean, median, standard deviation (SD), and 95% CI of the mean for continuous scale variables and frequency distributions with 95% CI around the estimate of proportions for categorical scale variables. Patient demographics and baseline characteristics were reported descriptively. The primary analysis was based on the full analysis set, defined as all patients who received at least 1 dose of sacubitril/valsartan. The primary efficacy outcome was assessed by the proportion of patients on sacubitril/valsartan 97/103 mg b.i.d. dose at 6 months of treatment. The 95% CI using binomial proportion was calculated for the estimate of the proportion to assess precision and make inferences to the target population. All the safety analyses were performed using the safety set, which included patients who received at least 1 dose of study medication. Statistical analyses were performed using SAS software (version 9.4).

Results

Study disposition

Overall, 322 patients were screened between March 8, 2016, and November 28, 2017. Of the 302 patients included and who received at least 1 dose of sacubitril/valsartan, 262 patients (86.8%) completed the study (Fig. 2). The most common reasons for discontinuation were AEs (5.3%), followed by death (3.0%), decision of patient/guardian (1.3%), loss to follow-up (1.0%), and withdrawal of consent (1.0%).

Table 1. Secondary endpoints

- Proportion of patients on sacubitril/valsartan who require down-titration after reaching the sacubitril/valsartan 97/103 mg b.i.d.
- Number of down-titration changes from sacubitril/valsartan 97/103 mg b.i.d. during 12 mo
- Proportion of patients who tolerate sacubitril/valsartan 97/103 mg b.i.d. at 6 and 12 mo
- Impact of sacubitril/valsartan on functional exercise capacity, as measured by the 6-min walk test, at 6 and 12 mo
- Time to uptitration of sacubitril/valsartan doses
- Duration of treatment on each dose of sacubitril/valsartan
- Proportion of patients receiving the guideline-recommended dose of β -blockers and mineralocorticoid receptor antagonists at baseline, 6 and 12 mo after treatment

b.i.d., twice daily.

Demographics and baseline characteristics

Among the overall patient population (N = 302), the mean age (SD) of the patients was 64.47 (10.77) years, and the majority were men (n = 240, 79.5%) and Caucasians (n = 271, 89.7%) (Table 2). A higher proportion of patients were in NYHA class II (n = 250, 82.8%) followed by 51 patients (16.9%) in class III. The mean (SD) EF at baseline was 29.47% (7.5). In most patients, ischemic HF was the underlying cause of HF (n = 160, 53%). More than half of the patients (n = 166, 55%) had not experienced prior hospitalization for HF.

Primary endpoint

Overall, 195 (64.6%) patients were on sacubitril/valsartan 97/103 mg b.i.d. after 6 months of treatment (95% CI: 59.18, 69.96), whereas 46 (15.2%) patients were on sacubitril/valsartan 49/51 mg b.i.d. and 29 (9.6%) patients on sacubitril/valsartan 24/26 mg b.i.d. (Table 3).

Secondary endpoints

At month 12, 188 (62.3%) patients remained on sacubitril/valsartan 97/103 mg b.i.d. and 44 (14.6%) patients were on sacubitril/valsartan 49/51 mg b.i.d. dose (Table 3). The mean

(SD) time for uptitration from 24/26 to 49/51 mg (n = 248), from 49/51 to 97/103 mg (n = 224), and from 24/26 to 97/103 mg (n = 200) was 21.44 (23.18), 27.37 (28.56), and 46.61 (36.94) days, respectively. Median time to reach sacubitril/valsartan 97/103 mg b.i.d. was 37 days (95% CI: 35, 42). Dose reduction was observed in 36 (11.9%) patients (95% CI: 8.27, 15.58) after attaining a dose of sacubitril/valsartan 97/103 mg b.i.d., whereas 31 (10.3%) patients required down-titration from a dose of sacubitril/valsartan 49/51 mg.

The assessment of the number of patients treated with the guideline-recommended HF therapies showed that 294 (97.4%) patients were treated with β -blockers, 165 (54.6%) patients were receiving mineralocorticoid receptor antagonists (MRAs) at baseline, whereas 228 (75.5%) patients were treated with ACEIs/ARBs at baseline before switching to sacubitril/valsartan. These results are consistent with previously reported data where 79.6% of patients with HF were treated with ACEIs/ARBs, whereas 85.6% were treated with β -blockers. Surprisingly, only 18% and 2% of patients were on optimal doses of β -blockers and MRAs, respectively.¹⁴ In the overall population, β -blockers, MRAs, and/or diuretics were prescribed to 298 (98.7%) patients at baseline, 272 (90.1%) patients at month 6, and 261 (86.4%) patients at month 12. However, there was a trend towards a decrease in the use of concomitant β -blockers (baseline: 97.4%, month 6: 88.4%, and month 12: 84.5%). A similar trend was observed for different β -blockers (alpha- and β -blocking agents [baseline: 30.5%, month 6: 27.8%, and month 12: 26.5%]; nonselective β -blocking agents [baseline: 1%, month 6: 1%, and month 12: 1%]; selective β -blocking agents [baseline: 65.9%, month 6: 59.6%, and month 12: 57%]). At the same time, the proportion of patients receiving optimal doses of β -blockers was low (baseline: 18.2%, month 6: 14.9%, and month 12: 14.2%). A similar trend was observed with concomitant MRAs (baseline: 54.6%, month 6: 45.4%, and month 12: 43%). A few patients were receiving optimal doses of MRA at baseline (1.7%), month 6 (1.3%), and month 12 (1.3%).

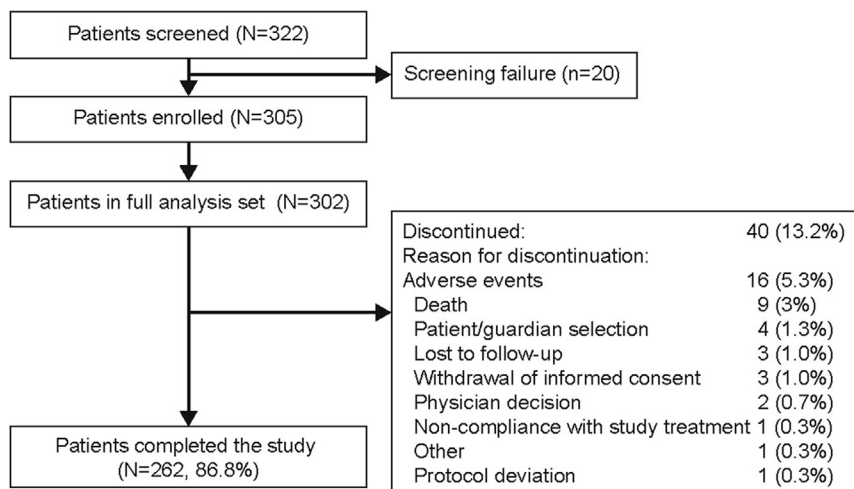


Figure 2. Patient disposition in Prospective, Multicenter, Open Label, Post-Approval Study Aimed at Characterizing the Use of LCZ696 at 97 mg Sacubitril/103 mg Valsartan bid in Patients With HFrEF (PARASAIL) study. Reasons for discontinuation are sorted by descending frequency for sacubitril/valsartan.

Table 2. Baseline characteristics

Characteristics	N = 302
Age (y), mean (SD)	64.47 (10.74)
Male (%)	79.5
Caucasian race (%)	89.7
BMI (kg/m ²), mean (SD)	31.42 (6.74)
Primary HF etiology, n (%)	
Ischemic	160 (53.0)
Nonischemic	142 (47.0)
Hypertensive	27 (8.9)
Diabetic	16 (5.3)
Alcoholic	12 (4.0)
Viral cardiomyopathy	15 (5.0)
Infectious cardiomyopathy	0
Peripartum	0
Drug induced	6 (2.0)
Hypertrophic cardiomyopathy	9 (3.0)
Idiopathic	58 (19.2)
NYHA class (%)	
Class II	82.8
Class III	16.9
Baseline SBP/DBP (mm Hg), mean	122/73
LVEF (%), mean (SD)	29.47 (7.50)
HF duration at baseline (y), mean (SD)	6.6 (5.8)
Baseline standard HF therapy (%)	
ACEI	57.9
ARB	18.2
β-Blockers (any dose/target dose)	97.4 / 18
MRA (any dose/target dose)	54.6 / 2
Diuretics	80.5
Comorbidities, n (%)	
Atrial fibrillation	96 (31.8)
Diabetes	66 (21.8)
Hypertension	173 (57.3)
Hypotension	3 (1.0)
Chronic kidney disease	9 (3.0)
Depression	27 (8.6)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

When analysed by the uptitration scheme, the number of patients in the swift scheme (n = 183) was higher than the patients in the conservative scheme (n = 42). A total of 66.1% patients in the swift scheme had 342 AEs, whereas 81.0% patients in the conservative scheme had 135 AEs, indicating that the proportion of patients having an AE is lower in the swift scheme subgroup. However, the incidence of AEs of interest was similar in both the schemes (swift: 12.3% and conservative: 11.9%). In contrast, it was reported

Table 3. Proportion of patients on sacubitril/valsartan at months 6 and 12

Dose (mg)	Sacubitril/valsartan (N = 302), % (n) (95% CI)
Month 6	
97/103	64.6 (195) (59.18, 69.96)
49/51	15.2 (46) (11.18, 19.28)
24/26	9.6 (29) (6.28, 12.93)
Month 12	
97/103	62.3 (188) (56.78, 67.72)
49/51	14.6 (44) (10.59, 18.55)
24/26	9.3 (28) (6.00, 12.54)

CI, confidence interval.

that 77 patients did not reach sacubitril/valsartan 97/103 mg b.i.d. and were in the “other” titration scheme. Of these, 64 (83.1%) had 234 AEs including 32 AEs of interest.

Other secondary endpoints

At baseline, the mean (SD) distance walked was 392.62 (139.33) m. At month 6, the mean distance walked was 418.45 (136.93) m. The mean distance walked in 6 minutes had increased by 11.99 (67.57) m at month 6 compared with baseline and the change in mean distance was statistically significant ($P = 0.0088$). At month 12, the mean distance walked was 419.34 (135.58) m. The mean distance walked in 6 minutes had increased by 8.19 (71.36) m at month 12 compared with baseline; however, the change in mean distance was not statistically significant ($P = 0.0910$).

Exploratory endpoints: QoL

Using the PGA, 158 (52.3%) patients experienced improvement in QoL (slight, moderate, and marked) at week 4, 177 (58.6%) patients at week 12, and 194 (64.2%) patients experienced improvement in symptoms at week 24. There was a trend of improvement at every time point (Fig. 3). The proportion of patients with worsening conditions was low and did not vary over time. When stratified by NYHA class, the proportion of patients belonging to NYHA class II (n = 250) reported an improved QoL over a longer time (week 4: 131 [52.4%]; week 12: 151 [60.4%]; and week 24: 166 [66.4%]). On the other hand, the proportion of patients belonging to NYHA class III reported that the QoL was unchanged for 27 (52.9%) patients at week 4, 26 (51.0%) patients at week 12, and 28 (54.9%) at week 24.

Overall, the MLHFQ total scores decreased from baseline to each time point ($P < 0.0001$, for all), indicating an improvement in QoL (Fig. 4). When stratified by NYHA class, patients with mild HF (NYHA class II) reported a greater reduction in MLHFQ scores ($P < 0.0001$ for each time point). Patients with NYHA class III demonstrated decreases in MLHFQ scores at week 4 ($P < 0.0001$) and week 12 ($P = 0.0013$) from baseline; however, it was not significant at week 24 ($P = 0.0507$) due to small sample size.

There was a significant improvement from baseline in the EQ-5D visual analogue score (VAS) at weeks 4, 12, and 24. A mean improvement in the VAS score of 2.96 (95% CI: 1.27, 4.65; $P = 0.0007$) at week 4, 3.79 (95% CI: 1.79, 5.79; $P = 0.0002$) at week 12, and 3.55 (95% CI: 1.55, 5.55; $P = 0.0006$) at month 6 were observed. In addition, there was an improvement from baseline in EQ-5D domain scores at different visits.

A significant change in the EQ-5D index scores from baseline to weeks 4 and 12 and month 6 was reported ($P < 0.05$). When stratified by NYHA class, patients with NYHA class II at baseline were more likely to show improvement over time than patients with NYHA class III at baseline, probably due to the small sample size of patients with NYHA class III compared with class II (Fig. 5). The VAS scores were consistent in terms of showing improvement in health status.

At baseline, most patients (82.8%) were in NYHA class II and approximately 16.9% were in NYHA class III. There were no patients in NYHA class I or class IV at baseline. During the first 12 weeks of treatment, the proportion of patients with NYHA class III and II decreased, with class III

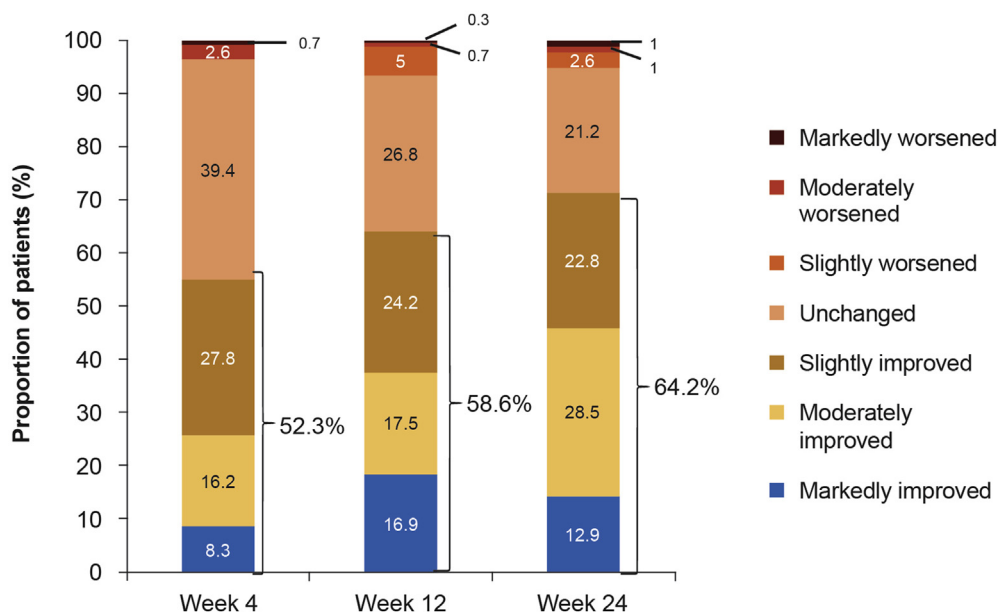


Figure 3. Proportion of patients with changes in patient global assessment (PGA) at weeks 4, 12, and 24 relative to baseline.

patients moving to class II and class II patients moving to class I (Fig. 6). Indeed, at week 12, 6.3% patients were in NYHA class I. Similarly, the same shift pattern in NYHA class was observed at month 6 and month 12, with an increase in the proportion of patients in NYHA class I (12.3% and 13.9%, respectively).

Safety

Overall, 215 (71.2%) patients in the safety set experienced at least 1 AE. Of these, 47 (15.6%) patients experienced a serious AE. The 3 most common AEs (≥ 20 patients) were dizziness (45 patients, 14.9%), hypotension (31 patients, 10.3%), and cough (20 patients, 6.6%). Hypotension (1.3%) and death (1.0%) were the common AEs leading to study discontinuation. In total, 9 deaths occurred during the study (representing 3% death at 1 year): 1 patient died of multiple organ failure, 3 patients died of cardiovascular events, and 5 patients died of noncardiovascular events. No deaths were considered to be related to the study drug.

In total, 87 (28.8%) patients experienced treatment-emergent AEs (TEAEs) related to the study drug. The most common ($\geq 2.0\%$) drug-related TEAEs were hypotension (23 patients, 7.6%), dizziness (19 patients, 6.3%), fatigue (8 patients, 2.6%), decreased BP, diarrhea, and nausea (6 patients, 2.0% each). The most common ($\geq 1.0\%$) TEAEs leading to study discontinuation were hypotension (4 patients, 1.3%) and death (3 patients, 1.0%).

Discussion

PARASAIL was a real-world 12-month study demonstrating the tolerability sacubitril/valsartan at 97/103 mg in Canadian patients with HFrEF. Patients were initiated on sacubitril/valsartan at the 24/26 mg dose and were titrated to the highest dose of 97/103 mg b.i.d. as per clinical judgement. Interestingly, approximately 64% patients achieved and remained on the highest target dose of sacubitril/valsartan 97/103 mg at 6 months (primary endpoint). A similar proportion of patients (around 62%) remained on the highest dose of sacubitril/

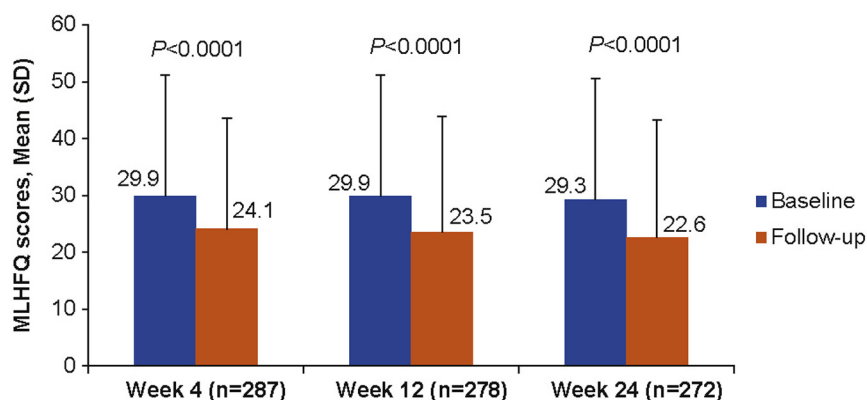


Figure 4. Changes in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores, by visit vs baseline. Note: Higher MLHFQ scores indicate poor quality of life. SD, standard deviation.

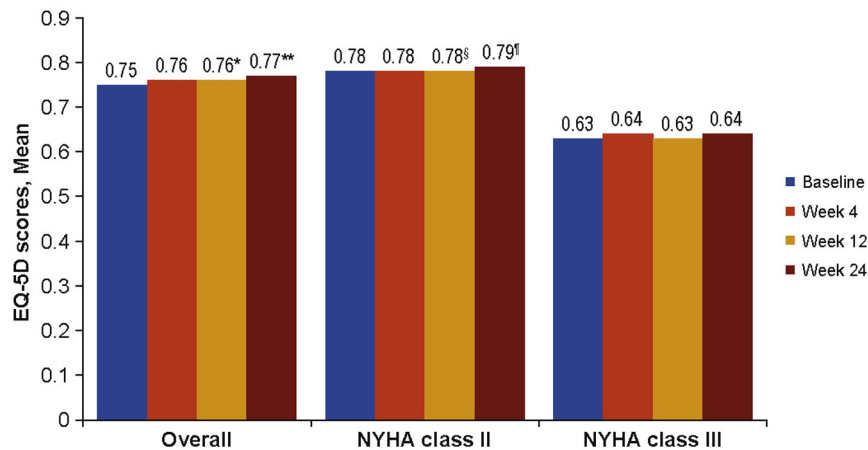


Figure 5. Change in Euro quality of life-5D (EQ-5D) index scores by visits: overall and stratified by New York Heart Association (NYHA) class II and III. * $P = 0.0013$; ** $P = 0.0032$; § $P = 0.0006$; ¶ $P = 0.0005$ (all values vs baseline).

valsartan 97/103 mg at the 12-month follow-up period. In addition, the observed median time for patients to uptitrate to 97/103 mg b.i.d. was 37 days, which represents a relatively short timeframe given the real-world nature of this trial where the titration scheme was performed as per the physician's clinical judgement.

The results of this study, obtained in the context of a real-world study design, are consistent with the observations from previous RCTs. The PARADIGM-HF study reported a mean (\pm SD) daily dose of sacubitril/valsartan of 375 ± 71 mg for a median duration of follow-up of 27 months for the sacubitril/valsartan treatment group.⁹ Differences in the study design and objectives between PARADIGM-HF and PARASAIL do not allow a direct comparison of the results of the 2 studies. Indeed, although in PARADIGM-HF the protocol-specified treatment start dose of sacubitril/valsartan was 49/51 mg b.i.d., in PARASAIL, the start doses of 24/26 and 49/51 mg b.i.d. were suggested as per approved Product Monograph. In addition, all patients enrolled in PARADIGM-HF were receiving a minimum required prestudy doses of ACEIs and ARBs, whereas 75.5% of patients enrolled in PARASAIL were treated with ACEIs or ARBs at any dose at baseline. Despite these differences in the study design between the 2 studies, interestingly the PARASAIL study results indicate that high doses such as the one reached for all patients in PARADIGM-HF could also be implemented and tolerated by a majority of patients in the real-world setting. More recent data from the TRANSITION study showed that the target dose of sacubitril/valsartan 97/103 mg was attained by 51% of patients in a hospitalization post-discharge setting at week 10.¹⁵ These results are consistent with the PARASAIL study results despite differences in the patient population between the 2 studies because the TRANSITION study was assessing the initiation of sacubitril/valsartan for patients with acute decompensated HF.

Other studies have also shown similar results. Indeed, the TITRATION study evaluated the tolerability of sacubitril/valsartan in patients with HFrEF and showed that approximately 76% patients achieved and remained on the target dose of sacubitril/valsartan 97/103 mg at the end of 12 weeks.¹² Similarly, a more recent retrospective study in patients with HFrEF showed that the target dose of

sacubitril/valsartan 97/103 mg was achieved in 65.3% of the total assessed population of 322 patients.¹⁶

A retrospective study from the USA, which included data from claims and review of medical records for 200 patients with HFrEF who initiated sacubitril/valsartan, showed that 17.4% patients achieved the maximum dose of sacubitril/valsartan 97/103 mg at 4 months.¹⁷ Another retrospective study using electronic medical records from the German IMS showed that most patients were initiated on the lowest dose of sacubitril/valsartan (24/26 mg) and only 8% of 25,264 patients with a first cardiologist prescription received the target dose of 97/103 mg b.i.d.¹⁴ However, differences in the study designs and in the patients' baseline characteristics such as mean age and prevalence of hypertension prevent any direct comparison with the current study. Overall, the target dose at the last prescription was observed in 20% patients in the general practitioners group and 21% patients in the cardiologists group.¹⁴ It is worthwhile to note that in the PARASAIL study, most of the participating investigators were cardiologists. In a retrospective study from a single tertiary HF clinic in Belgium (N = 120), it was observed that the mean (SD) total daily dose of sacubitril/valsartan achieved was 207 (117) mg in the entire cohort, which was significantly lower than that reported in the PARADIGM HF trial 375 (75) mg ($P < 0.001$).¹⁸

In the PARASAIL study, approximately 97%, 55%, and 76% of patients were receiving β -blockers, MRAs, and ACEIs/ARBs, respectively. These observations are consistent with previously reported data from a meta-analysis study regarding the proportion of patients with HF treated with guideline-recommended therapies.¹⁴ Further analysis of the PARASAIL data showed that 18% and 2% patients were on optimal doses of β -blockers and MRAs (data not shown). The above-mentioned meta-analysis study has demonstrated the potential benefits, including prevention of a significant number of HF-related deaths, if guideline-recommended HF therapies are adopted and applied in routine clinical practice as per guidelines.¹⁹ Also, it has been suggested that implementation efforts for these therapies to be successful in improving outcomes would need to be coupled with the use of optimal doses. In this context, PARASAIL has demonstrated

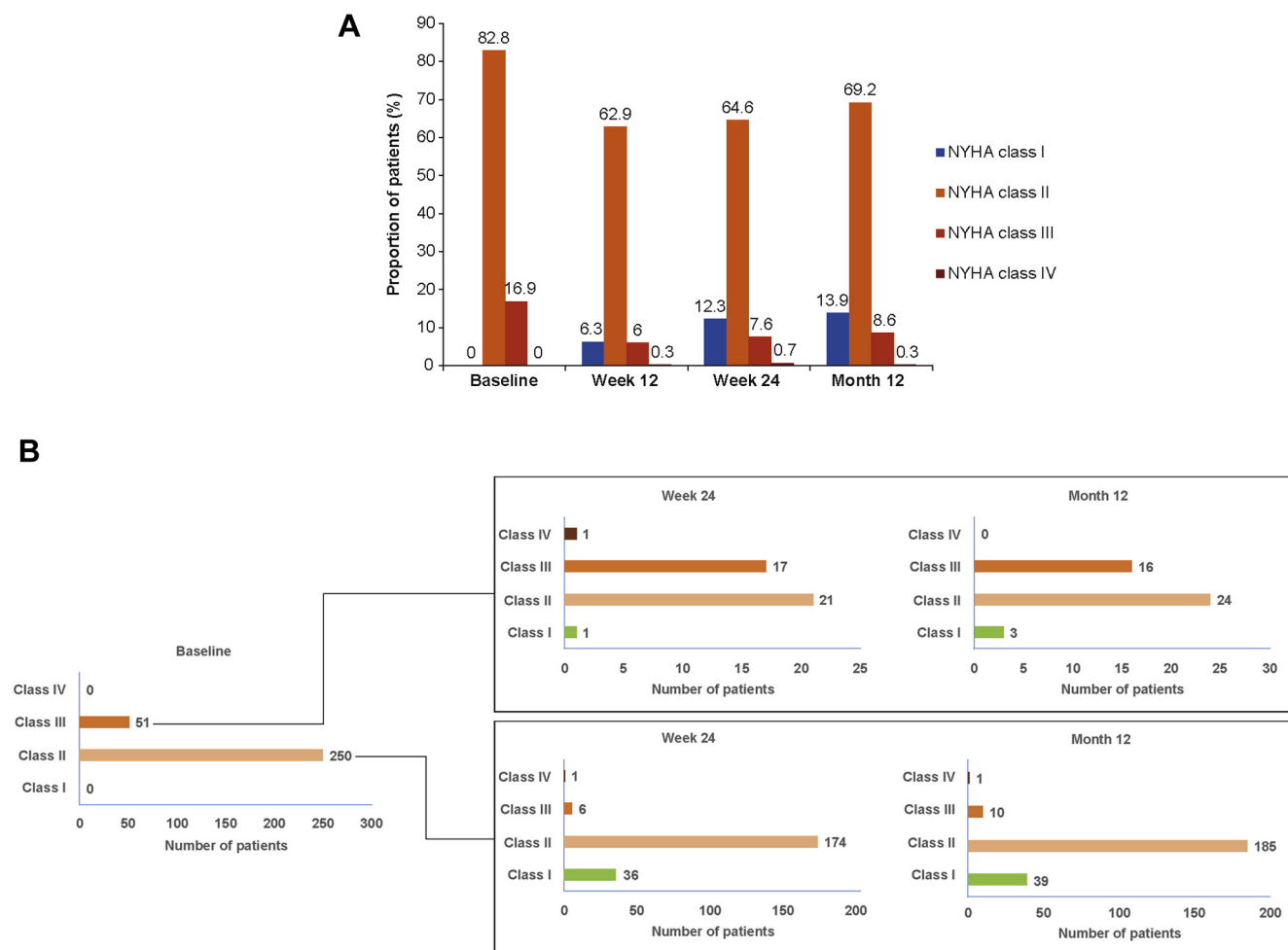


Figure 6. Number (%) of patients with New York Heart Association (NYHA) class, by visit. **(A)** Changes in NYHA Class from baseline to month 12 and **(B)** shift pattern in NYHA class from baseline to month 12.

that the optimal target dose of sacubitril/valsartan 97/103 mg could be achieved and tolerated in routine clinical care for the majority of Canadian patients with HFrEF, potentially resulting in the same benefits as reported in the previous pivotal trials.²⁰

Overall, the 6-MWT analysis showed a significant improvement for the overall population at 6 months. When stratified by the baseline NYHA class, this improvement at 6 months was more important and significant for patients with NYHA class II than for patients with NYHA class III. However, although statistically significant, the mean change in the walked distance of 11.99 m observed in the overall PARASAIL study population is modest compared with other study.¹¹

The PARASAIL study, which evaluated the improvement of QoL in patients with HFrEF using 3 different tools (PGA, MLHFQ, and EQ-5D), had shown a trend in the overall improvement in these patients, and this appears to occur in the early follow-up period (≤ 12 weeks). This study did not specifically evaluate the change in NYHA classification from baseline; however, there were numerically fewer patients in NYHA class II and there was an increase in the proportion of

patients in NYHA class I at week 12 and subsequent visits. This observation with all patient-reported outcomes showed an improvement trend in the overall patient symptoms and functional status.

In the PARASAIL study, only 9 deaths were reported representing 3% of the total study population during a 12-month follow-up period in comparison with a reported mortality rate of 30% at 1 year observed among patients diagnosed with HF in Canada.⁵ However, this difference may arise from the fact that the PARASAIL study population is limited to a subgroup (NYHA Class II and III with reduced EF) of the overall Canadian HF patient population. In addition, PARADIGM-HF has reported 17% death from any cause over a median duration of follow-up of 27 months in patients receiving sacubitril/valsartan. Differences in study design such as follow-up duration (12 months in PARASAIL vs 27 months in PARADIGM-HF), patient eligibility criteria (eg, NYHA Class II and III in PARASAIL vs NYHA Class I, II, III, and IV in PARADIGM-HF), and prior hospitalization for HF (45% in PARASAIL vs 62.3% in PARADIGM-HF) may be involved in the mortality rate difference between PARADIGM-HF and PARASAIL.

There are inherent limitations to consider in interpreting the findings of this real-world clinical study. First is the lack of a control group, thus reducing the generalizability of the findings, as the placebo effect of sacubitril/valsartan was not evaluated with a comparator arm. Also, this was an open-label study where investigators could follow their routine clinical practice in regard to treatment management and enroll patients irrespective of their baseline HF treatments. In addition, patients' eligibility was as per product monograph targeting patients with HF with NYHA class II and III not allowing therefore to generalize the study results to overall HF patient population in Canada. Finally, by design, there was no patient randomization, which may reduce the internal validity of the data.

Conclusions

The results of the PARASAIL study in a real-life setting showed that sacubitril/valsartan was well tolerated at the target dose of 97/103 mg. This was regardless of the titration scheme and that the majority of patients (65%) were maintained at the target dose of 97/103 mg b.i.d. Patient-reported outcomes demonstrated an overall improvement in QoL, which appeared to be greater in patients with baseline NYHA class II HF than baseline NYHA class III HF. In addition, the 6-MWT indicated a significant improvement in exercise capacity for patients with baseline NYHA class II at 6 months, but significance was lost at month 12. There were no new or unexpected safety signals evident from the AE profile.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2020.04.007>