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ORIGINAL RESEARCH ARTICLE

Effectiveness of Sacubitril/Valsartan in Reducing Hospitalizations in Older Belgian Adults with Heart Failure and Reduced Ejection Fraction: An Age-Stratified Study

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Abstract

Background Heart failure with reduced ejection fraction is increasingly prevalent in older adults, yet data on guideline-directed therapies in the oldest age groups remain limited.

Objective To assess outcomes of sacubitril/valsartan in adults aged ≥75 years, across age strata (≥75, ≥80, ≥85, ≥90 years; 75–79, 80–84, 85–89 years), focusing on cardiovascular, heart failure, and all-cause hospitalizations, and mortality.

Methods This retrospective study evaluated all patients aged ≥ 75 years in Belgium with chronic heart failure with reduced ejection fraction who started sacubitril/valsartan between 1 November, 2016 and 31 December, 2018.

Results A total of 1705 patients were divided into the following age groups: 75–79, 80–84, 85–89, and ≥ 90 years. Cardiovascular hospitalization rates significantly decreased across all age groups after sacubitril/valsartan initiation. Patients aged 75–79 years showed a reduction from 0.74 events/year (95% confidence interval [CI] 0.68–0.81) prior to treatment to 0.54 (95% CI 0.47–0.62, $p < 0.001$) after initiation. Rates fell from 0.73 (95% CI 0.66–0.80) to 0.53 (95% CI 0.44–0.65, $p < 0.001$) in those aged 80–84 years, from 0.62 (95% CI 0.52–0.74) to 0.44 (95% CI 0.35–0.57, $p < 0.01$) in those aged 85–89 years, and from 0.78 (95% CI 0.59–1.03) to 0.42 (95% CI 0.22–0.83, $p < 0.01$) in patients aged ≥ 90 years. Heart failure-related hospitalization rates also showed consistent reductions: 0.34 (95% CI 0.30–0.39) prior to treatment to 0.28 (95% CI 0.22–0.34) after initiation in patients aged 75–79 years, and from 0.38 (95% CI 0.33–0.43) to 0.30 (95% CI 0.23–0.39) in those aged 80–84 years (all $p < 0.05$). The rates decreased from 0.35 (95% CI 0.28–0.44) to 0.27 (95% CI 0.20–0.38, $p = 0.08$) in those aged 85–89 years and from 0.52 (95% CI 0.36–0.76) to 0.29 (95% CI 0.12–0.75, $p < 0.05$) in the oldest patients aged ≥ 90 years.

Conclusions Broader application of guideline-directed medical therapy in geriatric heart failure with reduced ejection fraction care should be prioritized.

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Key Points

This study examined the use of sacubitril/valsartan in older adults (aged ≥75 years) with heart failure and reduced ejection fraction in Belgium.

Cardiovascular hospitalization rates decreased significantly across all age groups after sacubitril/valsartan initiation, including patients aged ≥90 years. Heart failure hospitalization rates showed significant declines in all groups except for patients aged 85–89 years, who demonstrated a numerical improvement, but without statistical significance ($p = 0.08$).

The findings emphasize the benefits of expanding guideline-directed therapy for heart failure in older populations.

1 Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is a major contributor to morbidity and mortality in aging populations [1, 2]. In Europe, its prevalence increases sharply with age, affecting up to 10% of individuals aged ≥ 70 years [3]. Among these older adults, adverse outcomes are frequent, with hospitalization rates [4] approximating 20 per 100 patient-years and 2-year mortality rates exceeding 25% in those aged over 75 years [4].

Over the past three decades, the treatment landscape for HFrEF has evolved substantially. Guideline-directed medical therapies, including beta-blockers, renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and more recently, angiotensin receptor-neprilysin inhibitors (ARNIs) have consistently shown improvements in cardiovascular (CV) mortality and HF hospitalizations [5]. In the PARADIGM-HF trial, sacubitril/valsartan, the first-in-class ARNI, reduced the risk of CV death or HF hospitalization by 20% compared with enalapril [6]. Consequently, ARNI therapy has received a class I recommendation in international guidelines [7].

Individuals aged ≥ 75 years with HFrEF are underrepresented in randomized controlled trials. For instance, in PARADIGM-HF, only 18.6% of patients were aged ≥ 75 years, 7% were aged ≥ 80 years, and 1.4% were aged ≥ 85 years [8]. These trials often face limitations in generalizability because of enrollment criteria excluding individuals with frailty or significant comorbidities, leading to differences between trial outcomes and real-world clinical effectiveness [9]. Older patients frequently exhibit distinct impairments, such as renal dysfunction, and a heightened risk of hypotension, which can complicate treatment strategies and medication tolerability [10]. A more recent trial, with participants aged ≥ 75 years showing improvements in cardiac remodeling and functional health over 12 months, underscored the tolerability of sacubitril/valsartan but emphasized the clinical need for more robust data in this understudied demographic given the age-related HF pathophysiology and limited enrollment of frailer populations in trials [11].

Real-world evidence highlights the underuse of ARNIs in older populations despite their proven benefits. Roca et al. [12] observed that only 14.3% of individuals aged ≥ 75 years received ARNIs in their cohort, yet treatment was independently associated with lower mortality rates (hazard ratio [HR] 0.33; 95% confidence interval [CI] 0.19–0.57) and reduced HF hospitalizations. Similarly, a Medicare cohort study of patients aged ≥ 65 years found that ARNI treatment resulted in improved outcomes with lower risks of HF events and mortality compared with renin-angiotensin system inhibitors [13].

Despite compelling evidence, real-world uptake remains suboptimal however, particularly in older adults [14]. Multiple studies have highlighted the underuse of sacubitril/valsartan in clinical practice, with uptake rates below 10% in patients aged ≥ 80 years [15]. Concerns about tolerability, polypharmacy, and competing comorbidities likely contribute to therapeutic inertia, despite these patients bearing a disproportionately high event burden and potentially deriving a greater absolute benefit [16, 17]. Accordingly, age-specific real-world data are needed to guide clinical decision making in older adults. Although practice patterns may vary internationally, the pathophysiology and management principles of HFrEF are generally consistent across regions [18], as evidenced by shared treatment strategies outlined in international guidelines [19]. Previously, we examined the effectiveness of sacubitril/valsartan using Belgian national health insurance data and observed average reductions in CV and HF-related hospitalizations among patients aged ≥ 75 years [20]. However, that analysis reported aggregated outcomes, without stratification by age group or hospitalization type. Given the clinical heterogeneity among older adults, additional granularity is required to inform and refine clinical practice. The present study builds on that work by re-examining the cohort with a specific focus on hospitalizations because of CV and HF causes, as well as all-cause hospitalizations and mortality across older age subgroups, including patients aged ≥ 85 and ≥ 90 years, to determine whether the clinical benefits of sacubitril/valsartan extend to the oldest-old and to compare these findings with trial-based benchmarks.

2 Methods

2.1 Design and Setting

This nationwide retrospective non-interventional cohort study utilized patient-level linkage of integrated electronic healthcare data from Belgium. Data sources included administrative payer claims, national health registries, pharmacy dispensing records, and medical records. In Belgium, reimbursement for sacubitril/valsartan requires meeting all of the following criteria: (i) age ≥ 18 years; (ii) symptomatic HFrEF, defined as New York Heart Association class II–IV, (iii) left ventricular ejection fraction ≤ 35% confirmed by echocardiography; (iv) prior treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; and (v) initiation and prolongation by a cardiologist or internist [20].

2.2 Ethics

This secondary analysis of pseudonymized data was conducted in accordance with applicable regulations and approved by the Belgian Data Protection Authority [20]. The need for informed consent was waived under national guidelines. All the protocols including the collection of data complied with the European General Data Protection Regulations. The purpose of this study and data processing were detailed in a privacy notice made available to the healthcare professional community in Belgium, aimed at informing patients treated with sacubitril/valsartan, per request of the Belgian Data Protection Authority [20].

2.3 Study Population

The dataset included all adult patients in Belgium with chronic symptomatic HFrEF who initiated sacubitril/valsartan between 1 November, 2016 and 31 December, 2018, irrespective of their prior medical history or length of follow-up ($n = 5446$) [20]. Data were obtained by Sciensano via the healthdata.be platform, with a follow-up period (for mortality) of beyond 6 years, ending on 16 March, 2023 [20]. Pseudonymized data were compiled into a national registry of real-world data ("Registry") [20]. Further methodological details, including the technical architecture of the platform as well as the description of the databases and variables, are provided in the ESM [20].

Exclusions applied were: (i) patients without records in the Intermutualistic Agency database (i.e., no evidence that sacubitril/valsartan was dispensed); (ii) patients without additional data beyond Intermutualistic Agency records (i.e., no information regarding follow-up); (ii) patients who initiated the study medication on 31 December, 2018 (i.e., unable to contribute follow-up information); and (iv) patients whose death date in the National Register of Natural Persons preceded the initiation of sacubitril/valsartan.

The final analytic cohort consists of 5408 patients. The current analysis utilized a refined dataset with expanded coverage of clinical variables relevant to the study objectives investigated in the prior analysis (dataset #2, as described in Maury et al. [20]). This analysis focuses on the 1705 patients in the cohort aged ≥ 75 years.

2.4 Outcomes

The analysis builds on prior work in patients aged ≥ 75 years by providing a more granular evaluation of clinical outcomes across age subgroups. These subgroups include patients aged ≥ 75 years, ≥ 80 years, ≥ 85 years, and ≥ 90 years, as well as segmented groups such as 75–79 years, 80–84 years, and 85–89 years.

The National Intermutualistic College database was utilized to quantify the number of reimbursement requests for sacubitril/valsartan submitted per patient between 1 November, 2016 and 31 December, 2018. Each reimbursement request corresponded to a 12-month treatment period.

We assessed hospitalization rates (any cause, and CV and HF specific) and all-cause mortality rates. Hospitalizations were classified as CV or HF related based on admission (International Classification of Diseases, 10th Revision), defined using diagnosis codes from hospital records [20], as listed in the ESM. Hospitalization data were censored on 31 December, 2019 and mortality data on 16 March, 2023 in case no event was observed. This discrepancy is explained by the limited availability of more recent hospitalization data.

2.5 Adverse Events

A descriptive analysis of adverse events (AEs) leading to sacubitril/valsartan discontinuation or interruption was conducted using a separate dataset provided by Novartis. This dataset includes 257 AE cases reported in Belgium between November 2016 and December 2018, retrieved in ARGUS pharmacovigilance software, i.e., all reported AE cases of discontinuation or interruption with patient age available. It is distinct from the claims-based cohort used for the primary analyses. The timeline November 2016–December 2018 is similar to the treatment initiation period for the entire main cohort described in Maury et al. [20]. Nineteen cases were spontaneously reported by healthcare professionals, while the remaining 238 cases were obtained in a monitored setting, such as through a non-interventional study or a patient-oriented program. For each case, event descriptions and seriousness were assessed. The AEs were verbatim reported

(rather than coded using the International Classification of Diseases, 10th Revision classification).

2.6 Statistical Analyses

Pseudonymization and linkage across multiple databases accessed via healthdata.be ensured that each patient was included only once, at the time of their first sacubitril/valsartan prescription within the inclusion period. Data were complete and no imputation was required.

All-cause mortality rates were estimated using Poisson regression with patient death as the outcome and each patient's follow-up time (in years) included as an offset term. Annualized mortality rates and corresponding 95% CIs were reported. Patients were followed from treatment initiation until death or censoring (16 March, 2023) [20].

Hospitalization incidence (all cause, CV, HF specific) was estimated similarly. The number of hospitalizations per patient served as the outcome. The offset comprised time at risk, calculated from treatment start to either death or 31 December, 2019, minus days hospitalized. To evaluate changes in event rates following sacubitril/valsartan initiation, a within-patient pre-post comparison was performed using Poisson regression with robust standard errors to account for the dependency within a patient. Annual hospitalization rates with corresponding 95% CIs were calculated for both periods and *p* values are reported for the pre-post comparison.

Patients who first received sacubitril/valsartan in the hospital and died during the same hospitalization were not considered at risk for hospitalization and therefore not included in the analysis. Hospital diagnoses prior to treatment initiation were available for > 85% of patients, starting from 30 to 720 days prior to start of sacubitril/valsartan, between 1 November, 2016 and treatment start.

Baseline characteristics are reported as mean ± standard deviation (SD) for continuous variables and counts with percentages for categorical variables. The Wald (*z*) test on the log rate ratio was used to identify differences in CV and HF hospitalization rates before and after initiation of sacubitril-valsartan between 5-year age subgroups. For categorical variables (e.g., sex distribution [male/female], presence/absence of requests, and occurrence of AEs), comparisons were performed with the use of Fisher's exact test. A two-sided *p* value < 0.05 was considered statistically significant. No adjustments were made for multiple comparisons given the exploratory nature of the study. Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA) or Prism 10.1.2 (GraphPad Software, Boston, MA, USA).

3 Results

The mean (± SD) age in the cohort of 1705 patients (aged ≥ 75 years) was 80.7 (± 4.2) years, and 28.6% were female (Table 1). Patient demographic characteristics across age groups are summarized in Tables 1 and 2. A progressive decline in the proportion of male patients was observed with increasing age. In the cohort aged 75–79 years, men comprised 74.49% (584/784) of the population. This proportion declined to 71.52% (427/597) in the 80–84 years of age group (not significant), followed by 64.53% (171/265) in the 85–89 years of age group ($p = 0.003$, compared to the 75–79 years of age group, Fisher's exact test). Among patients aged ≥ 90 years, men accounted for 61.02% (36/59, $p = 0.031$, compared to the 75–79 years of age group, Fisher's exact test).

The number of treatment requests during the study period remained consistent across the 75–79, 80–84, and 85–89-year age groups, each of which included more than 100 patients, with no significant differences observed (Fisher's exact test, Table 2). This suggests no apparent bias in treatment access related to age.

We then investigated changes in the risk of hospitalization for any cause, as well as hospitalization because of

Table 1 Profile of included patients, with patients aged ≥75 years stratified by incremental age thresholds

Demographics	Statistics	≥ 75 years	≥ 80 years	≥ 85 years	≥ 90 years
Total number of patients	*N*	1705	921	324	59
Age (years)	[*n*] Mean (SD)	[1705] 80.7 (4.2)	[921] 83.8 (3.3)	[324] 87.5 (2.5)	[59] 91.6 (2.1)
Sex					
Male	*n*/*N* (%)	1218/1705 (71.44%)	634/921 (68.84%)	207/324 (63.89%)	36/59 (61.02%)
Female	*n*/*N* (%)	487/1705 (28.56%)	287/921 (31.16%)	117/324 (36.11%)	23/59 (38.98%)
Number of requests					
1	*n*/*N* (%)	784/1059 (74.03%)	398/526 (75.67%)	128/161 (79.50%)	22/23 (95.65%)
2	*n*/*N* (%)	269/1059 (25.40%)	126/526 (23.95%)	33/161 (20.50%)	1/23 (4.35%)
3	*n*/*N* (%)	6/1059 (0.57%)	2/526 (0.38%)	0/161 (0.00%)	0/23 (0.00%)

SD standard deviation

Table 2 Profile of the included advanced-age patients, with patients aged ≥ 75 years stratified by 5-year age groups

Demographics	Statistics	75–79 years	80–84 years	85–89 years
Total number of patients	*N*	784	597	265
Age (years)	[*n*] Mean (SD)	[784] 77.1 (1.4)	[597] 81.8 (1.4)	[265] 86.6 (1.4)
Sex				
Male	*n*/*N* (%)	584/784 (74.49%)	427/597 (71.52%)	171/265 (64.53%)
Female	*n*/*N* (%)	200/784 (25.51%)	170/597 (28.48%)	94/265 (35.47%)
Number of requests				
1	*n*/*N* (%)	386/533 (72.42%)	270/365 (73.97%)	106/138 (76.81%)
2	*n*/*N* (%)	143/533 (26.83%)	93/365 (25.48%)	32/138 (23.19%)
3	*n*/*N* (%)	4/533 (0.75%)	2/365 (0.55%)	0/138 (0.00%)

SD standard deviation

CV reasons or HF among patients aged ≥ 75 years (Table 1 of the ESM). The annual rate of hospitalizations for any cause showed no significant change, estimated at 1.71 (95% CI 1.62; 1.81) pre-treatment compared with 1.67 (95% CI 1.56; 1.79) post-treatment ($p = 0.5$). However, the annual CV hospitalization rate decreased from 0.72 (95% CI 0.68–0.76) prior to treatment to 0.52 (95% CI 0.47–0.58) after treatment initiation ($p < 0.0001$; Table 3, Table 1 of the ESM), with consistent reductions observed across age subgroups, including those aged ≥ 80, ≥ 85, and ≥ 90 years ($p < 0.01$).

In subgroup analyses, annual CV hospitalization rates demonstrated robust reductions across the subgroups aged 75–79 years, 80–84 years, and 85–89 years. Rates decreased from 0.74 (95% CI 0.68–0.81), 0.73 (95% CI 0.66–0.80), and 0.62 (95% CI 0.52–0.74) prior to treatment to 0.54 (95% CI 0.47–0.62), 0.53 (95% CI 0.44–0.65), and 0.44 (95% CI 0.35–0.57) after initiation, respectively ($p < 0.01$; Table 4).

Sacubitril/valsartan also demonstrated consistent effectiveness in reducing HF-related hospitalizations in older patients. In patients aged ≥ 75 years, the annual HF hospitalization rate declined significantly from 0.36 (95% CI 0.33–0.39) prior to treatment to 0.28 (95% CI 0.24–0.33) after initiation ($p < 0.0001$; Table 5, Table 1 of the ESM).

Similar reductions were observed in subgroups, with hospitalization rates dropping from 0.38 (95% CI 0.34–0.42) to 0.29 (95% CI 0.24–0.36) [$p < 0.001$] for patients aged ≥ 80 years, from 0.38 (95% CI 0.32–0.47] to 0.28 (95% CI 0.20–0.38) [$p < 0.01$] for patients aged ≥ 85 years, and from 0.52 (95% CI 0.36–0.76) to 0.29 (95% CI 0.12–0.75) [$p < 0.05$] for patients aged ≥ 90 years, the group demonstrating the greatest reduction in HF hospitalizations (Table 5).

Additionally, in narrower age brackets (75–79 years, 80–84 years), annual HF hospitalization rates demonstrated consistent reductions. Patients aged 75–79 years experienced significantly reductions from 0.34 (95% CI 0.30–0.39) prior to treatment to 0.28 (95% CI 0.22–0.34) after initiation ($p < 0.05$), while patients aged 80–84 years showed a significant decline from 0.38 (95% CI 0.33–0.43) to 0.30 (95% CI 0.23–0.39) [$p < 0.05$]. The rate observed in patients aged 85–89 years decreased from 0.35 (95% CI 0.28–0.44) to 0.27 (95% CI 0.20–0.38) after initiation ($p = 0.08$; Table 6), showing that the decrease in patients aged ≥ 85 years ($p < 0.01$) was mainly driven by that of patients aged ≥ 90 years ($p < 0.05$; Table 5).

In parallel, an analysis of 257 AEs leading to treatment interruption or discontinuation in Belgium (November 2016–December 2018) provided 168 serious events (65.4%) and 89 non-serious events (34.6%). The identified AE types included cardiac events encompassing HF (including worsening, acute congestive episodes, and cardiogenic shock), atrial fibrillation, ventricular tachycardia, acute lung edema,

Table 3 Changes in annual rates of CV hospitalizations in patients aged ≥ 75 years stratified by incremental age thresholds

CV hospitalizations	Statistics	≥ 75 years	≥ 80 years	≥ 85 years	≥ 90 years
Total number of patients	*N*	1705	921	324	59
Annual CV hospitalization rate (hospitalizations/year) prior to sacubitril/valsartan	Est. (95% CI)	0.72 (0.68–0.76)	0.70 (0.64–0.76)	0.65 (0.56–0.76)	0.78 (0.59–1.03)
Annual CV hospitalization rate (hospitalizations/year) after initiation	Est. (95% CI)	0.52 (0.47–0.58)	0.50 (0.43–0.59)	0.44 (0.35–0.56)	0.42 (0.22–0.83)
Comparison before vs after initiation	*P* value	< 0.0001	< 0.0001	0.0002	0.0053

CI confidence interval, *CV* cardiovascular, *Est.* estimate

Table 4 Changes in annual rates of CV hospitalizations in patients aged ≥ 75 years stratified by 5-year age groups

CV hospitalizations	Statistics	75–79 years	80–84 years	85–89 years
Total number of patients	*N*	784	597	265
Annual CV hospitalization rate (hospitalizations/year) prior to sacubitril/valsartan	Est. (95% CI)	0.74 (0.68–0.81)	0.73 (0.66–0.80)	0.62 (0.52–0.74)
Annual CV hospitalization rate (hospitalizations/year) after initiation	Est. (95% CI)	0.54 (0.47–0.62)	0.53 (0.44–0.65)	0.44 (0.35–0.57)
Comparison before vs after initiation	*P* value	< 0.0001	< 0.0001	0.0043

CI confidence interval, *CV* cardiovascular, *Est.* estimate. When comparing CV hospitalization rates across age groups 75–79, 80–84, 85–89, and ≥ 90 years, we found no significant differences either before or after treatment initiation.

Table 5 Changes in annual rates of HF hospitalizations in patients aged ≥ 75 years stratified by incremental age thresholds

HF hospitalizations	Statistics	≥ 75 years	≥ 80 years	≥ 85 years	≥ 90 years
Total number of patients	*N*	1705	921	324	59
Annual HF hospitalization rate (hospitalizations/year) Prior to sacubitril/valsartan	Est. (95% CI)	0.36 (0.33–0.39)	0.38 (0.34–0.42)	0.38 (0.32–0.47)	0.52 (0.36–0.76)
Annual HF hospitalization rate (hospitalizations/year) after initiation	Est. (95% CI)	0.28 (0.24–0.33)	0.29 (0.24– 0.36)	0.28 (0.20–0.38)	0.29 (0.12–0.75)
Comparison before vs after initiation	*P* value	< 0.0001	0.0008	0.0086	0.0254

CI confidence interval, *Est.* estimate, *HF* heart failure

Table 6 Changes in annual rates of HF hospitalizations in patients aged ≥ 75 years stratified by 5-year age groups

HF hospitalizations	Statistics	75–79 years	80–84 years	85–89 years
Total number of patients	*N*	784	597	265
Annual HF hospitalization rate (hospitalizations/year) prior to sacubitril/valsartan	Est. (95% CI)	0.34 (0.30–0.39)	0.38 (0.33–0.43)	0.35 (0.28–0.44)
Annual HF hospitalization rate (hospitalizations/year) after initiation	Est. (95% CI)	0.28 (0.22–0.34)	0.30 (0.23–0.39)	0.27 (0.20–0.38)
Comparison before vs after initiation	*P* value	0.0126	0.0203	0.0802

CI confidence interval, *Est.* estimate, *HF* heart failure. When comparing HF hospitalization rates across age groups 75–79, 80–84, 85–89, and ≥90 years, we found no significant differences either before or after treatment initiation, except for patients aged ≥90 presenting higher baseline HF hospitalization rates than those aged 75–79 (P = 0.04).

and cardiac decompensation. Renal events included acute kidney insufficiency (both chronic and prerenal failure), hyperkalemia, and deterioration of renal function. Pulmonary events included bronchopneumonia, respiratory insufficiency, and dyspnea episodes. Infectious events were also reported. Other serious AEs included severe cases of hypotension, orthostatic syncope, and hematoma. In contrast, non-serious AEs primarily included fatigue, dizziness, edema, weight changes, skin rash or itching, diarrhea, bronchitis, mild creatinine abnormalities, and palpitations. The average age of patients in the dataset was 67.4 ± 11.1 years (mean ± SD), which is similar to the full cohort in Maury et al. [20], with a mean ± SD age of 67.8 ± 12.1 years. Among these 257 AE cases reported, 78 (30.3%) involved patients aged ≥ 75 years. This proportion did not differ from the proportion of patients aged ≥ 75 years in the overall treated cohort (31.5%) [Fisher's exact test, $p = 0.54$].

While all-cause mortality increased with age, with the proportion of deaths rising from 59.9% in patients aged ≥ 75 years to 76.3% in patients aged ≥ 90 years, this trend remained consistent with the expected progression of age-related mortality (Tables 2–3 of the ESM). Annual death rates, adjusted for follow-up time, ranged from 0.13 to 0.30 across all age groups (Table 3 of the ESM). Although the follow-up duration was shorter in the oldest subgroup (mean ± SD: 2.59 ± 1.87 years in adults aged ≥ 90 years vs 3.39 ± 1.88 years in the overall ≥ 75-year population), consistent reductions in hospitalization rates were observed across all subgroups (see Tables 3, 4, 5), with annual mortality rates remaining within an expected range for this population.

4 Discussion

This nationwide real-world study evaluated outcomes following initiation of the ARNI sacubitril/valsartan in Belgian adults aged ≥ 75 years with HFrEF. Using linked national claims, hospitalization, and dispensing data, 1705 patients (mean age 80.7 years, SD 4.2) were followed. Initiation of sacubitril/valsartan was associated with clinically meaningful reductions in CV and HF-related hospitalizations, without excess mortality, even among the oldest and most symptomatic patients. These findings reinforce the effectiveness and tolerability of sacubitril/valsartan in a population underrepresented in landmark trials [1].

Annual CV hospitalization rates declined from 0.72 to 0.52 events/year for CV causes ($p < 0.0001$), and from 0.36 to 0.28 events/year for HF ($p < 0.0001$). Remarkably, CV hospitalization rates decreased significantly across all age groups after sacubitril/valsartan initiation, including patients aged ≥ 90 years. Heart failure hospitalization rates showed significant declines in all groups except for patients aged 85–89 years, who demonstrated a numerical improvement, without statistical significance ($p = 0.08$). The significant decline in HF hospitalization rates observed in the oldest patient group (aged ≥ 90 years, $p < 0.05$), which contributes notably to the overall reductions seen in patients aged ≥ 85 years ($p < 0.01$), supports its use as an effective therapeutic option in this age group. Mortality rates remained within expected ranges, with a crude mortality rate of 59.9% over 3.4 years and annualized death rate of 0.18 deaths/year (95% CI 0.15–0.21). Median survival ranged from 4.43 years (age 75–79 years) to 2.66 years (age 85–89 years), consistently aligned with life expectancy in this age group [2, 4].

In the seminal trial PARADIGM-HF, involving 47 countries, spread across three main regions America, Europe, and Asia, sacubitril/valsartan reduced the risk of a first HF hospitalization by 21% compared with enalapril (HR 0.79; 95% CI 0.71–0.89), in a population with a mean age of 63.8 years [6]. While HRs were not calculated in the present analysis, the absolute reductions (~ 20 to 25%) observed in patients aged ≥ 75 years suggest comparable clinical utility in this older higher-risk population with data up to ≥ 90 years of age. In a post-hoc analysis of the PARADIGM-HF trial, patients were categorized by age to show that its impact on HF hospitalization consistently achieved significance across all age groups (< 55, 55–64, 65–74, and ≥ 75 years) [8]. This observation now applies to real-world patients segmented groups such as aged 75–79 years, 80–84 years, and ≥ 90 years. Notably, the post-treatment HF hospitalization rate in our cohort was 0.28 events per patient-year, approximately four times higher than the annualized rate observed in PARADIGM-HF's ARNI arm (~ 7% annually). This discrepancy likely reflects differences in patient age, inclusion criteria, follow-up intensity, and reporting metrics (annualized vs cumulative incidence).

The benefit of sacubitril/valsartan builds on prior therapeutic milestones. The CONSENSUS trial showed angiotensin-converting enzyme inhibitors reduced mortality by 27% in patients with severe HF [21]. PARADIGM-HF demonstrated that sacubitril/valsartan provided incremental benefits beyond angiotensin-converting enzyme inhibition [6]. In a recent network meta-analysis, sacubitril/valsartan ranked among the most effective therapies for reducing HF hospitalizations in HFrEF [5]. Furthermore, data from PARADIGM-HF estimated a 5-year number needed to treat of just 11 to prevent one CV death or HF hospitalization compared with enalapril [22]. Supporting its real-world relevance, a Markov decision process model indicated that, even after accounting for "real-world" rates of drug discontinuation, initiating sacubitril/valsartan at discharge provided a significant survival advantage that persisted across increasing age [23]. These findings support the role of sacubitril/valsartan as a foundational therapy in modern HF care.

Time to benefit is particularly relevant in older adults, who often face limited life expectancy and competing risks [20, 24, 25]. In PARADIGM-HF, event curves for HF hospitalization and CV death began to diverge within 30 days of treatment initiation [25]. Although our study did not include time-to-event analyses, hospitalization rates were already reduced within the first year of treatment, supporting early clinical benefit. These findings underscore the importance of prompt initiation, particularly in older adults with constrained life expectancy [11, 12, 25, 26]. It must be noted that the change in hospitalization rate may be influenced by a change in risk of hospitalization because of disease progression, regression to the mean, or mortality.

Despite consistent evidence on its efficacy, safety, and timeliness, sacubitril/valsartan remains underused in older adults. In the Swedish Heart Failure Registry, less than 10% of patients with HFrEF aged ≥ 80 years were prescribed an ARNI [27]. In contrast, ARNI usage was higher among younger age groups, with 17–25% of patients aged < 80 years receiving this treatment. These findings highlight differences in the use of evidence-based therapies across age strata in patients with HFrEF [27]. An accompanying analysis found that older age independently predicted ARNI non-initiation, even after adjusting for comorbidities [15]. These patterns suggest age-related therapeutic inertia rather than clinical ineligibility [16]. Our findings counter this trend, demonstrating the feasibility and benefit of ARNI use in patients aged ≥ 75 years, including those aged ≥ 90 years. Moreover, the analysis of AEs leading to treatment interruption or discontinuation in Belgium (November 2016–December 2018) suggests that older adults do not experience a higher burden of AEs. Emerging evidence from real-world studies suggests that sacubitril/valsartan is well tolerated among older adults

[28, 29]. The utilization of the US Food and Drug Administration database of safety reports (FAERS) demonstrated that AEs such as hypotension, acute kidney injury, hyperkalemia, and angioedema were reported at comparable rates between adults aged < 75 years and those aged ≥ 75 years [29]. For example, the rate of hypotension leading to discontinuation was relatively low, at 1.8%, confirming the safety of its use in this population [29].

Addressing this under-utilization gap requires implementation strategies inspired by trials like STRONG-HF, which showed that rapid up-titration of guideline-directed medical therapies within weeks of discharge led to a 34% relative reduction in all-cause death or HF readmission at 180 days (HR 0.66; 95% CI 0.50–0.88). Early and structured therapy optimization is essential, especially in older patients at high risk. Achieving this in practice will require a multidisciplinary collaboration [24, 30]. Pharmacist-led medication reviews, nurse-driven follow-up, and physician oversight are key to ensuring safe and effective titration. Embedding ARNI initiation within team-based HF pathways may help overcome clinical inertia and improve uptake, particularly in care settings dealing with complex older adults [17]. Locoregional care initiatives such as "Zorgzaam Leuven," may offer scalable models for mapping patients, coordinating care, and implementing shared medication protocols [31].

Several limitations merit consideration. First, this was a non-randomized within-subject comparison, limiting causal inference. The research did not include a control group of patients who were treated solely with the standard of care without sacubitril/valsartan, which is important for determining a reliable baseline to assess the effectiveness of the treatment. Second, medication exposure was inferred from reimbursed dispensing data, which may overestimate treatment adherence and exposure. Additionally, long-term persistence and data on concurrent medical therapies (e.g., beta-blockers, MRAs) were unavailable. However, we observed that over one fourth of older adults remained on ARNI treatment at 12 months (Table 1), in line with our previous analysis showing that 27% of patients aged ≥ 75 years had a second request for reimbursement (12 more months), and 2% a third request (i.e. 24 more months) within the first 26 months after market introduction [20]. Further, AE data were obtained from a separate pharmacovigilance dataset, limited to 257 cases with known age. While the proportion of older adults (aged ≥ 75 years) among these reports (30.3%) was similar to that of the registry (31.5%), the small sample size, reliance on spontaneous reporting, and the lack of clinical detail limit firm conclusions regarding age-specific tolerability. Third, unmeasured confounders, such as frailty, renal function, and polypharmacy, may also have influenced outcomes. Fourth, hospitalization events were classified using International Classification of Diseases, 10th Revision codes at admission, which is standard, but subject to potential misclassification. Both hospitalization rates and absolute numbers are provided for patients aged 75 years or older, but the lack of granularity from stratification by incremental age thresholds limits the ability to analyze event distribution and understand evolving patterns across age subgroups. Moreover, although the mortality follow-up extended beyond 6 years, hospitalization data were limited to a shorter period, censored in December 2019 because of database update limitations. Fifth, between November 2016 and December 2018 (i.e., initial 26 months following the product's market introduction), 39.6% of patients in the full cohort ($n = 5446$) were prescribed the lowest sacubitril/valsartan dose (24/26 mg), 36.9% the median dose (49/51 mg), and 23.9% the highest dose (97/103 mg), irrespective of age (data provided by the National Federation of Independent Pharmacists Algemene Pharmaceutische Bond, APB, not shown). This pattern suggests a conservative dose selection was common and not age stratified, potentially limiting insights into dose-dependent tolerability in older adults [20]. Last, it is important to note that this analysis was conducted within Belgium. While this provides valuable insights into real-world ARNI usage and outcomes for a focused population, the generalizability of findings may be somewhat limited because of regional practice patterns and prescribing behaviors. Nevertheless, the consistency of observed treatment persistence and hospitalization rates with broader international trends [18] suggests that these findings are still highly relevant and reflective of global HFrEF management principles.

Future research should focus on integrating administrative data with clinical registries or electronic health records to better characterize patient phenotypes, treatment trajectories, and frailty. Prospective cohort studies and pragmatic trials could help clarify how treatment response varies by age, comorbidity, or social determinants. Implementation research targeting barriers to ARNI initiation, especially in older adults, is indicated. Regional networks, such as those in Leuven [31], provide real-world testbeds for piloting and scaling such approaches.

5 Conclusions

In this nationwide real-world cohort of Belgian adults aged ≥ 75 years with HFrEF, sacubitril/valsartan was associated with clinically meaningful reductions in CV and HF-related hospitalizations, with no excess mortality, even among the oldest and most symptomatic patients. These findings support a broader application of guideline-directed therapy in geriatric HF care and reaffirm the foundational role of sacubitril/valsartan. Given its early and sustained benefits, supported by team-based models, broader adoption in aging health systems should be prioritized.

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Declarations

Conflict of interest Eléonore Maury and Mieke Jansen are employees of the sponsor. Ann Belmans and Kris Bogaerts were paid by the sponsor via their institution to perform the analyses. Lorenz Van der Linden has no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This secondary analysis of pseudonymized data was conducted in accordance with applicable regulations and approved by the Belgian Data Protection Authority. The need for informed consent was waived under national guidelines. All the protocols including the collection of data complied with the European General Data Protection Regulations. The purpose of this study and data processing were detailed in a privacy notice made available to the healthcare professional community in Belgium, aimed at informing patients treated with sacubitril/valsartan, per request of the Belgian Data Protection Authority.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Additional information is available from the corresponding author (eleonore.maury@novartis.com) upon reasonable request. The information presented in this paper combines several Belgian administrative databases. The data use is subject to the European Union's General Data Protection Regulation. Patient-level data were available via the healthdata.be in the framework of a managed entry agreement between Novartis and the payer institute National Institute for Health and Disability Insurance (NIHDI-RIZIV-INAMI). Access to data was restricted to address uncertainties in the context of a managed entry agreement and related publication. Patient-level data may not be shared publicly or transferred because of ethical reasons and security considerations.

Code availability Not applicable.

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