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RESEARCH ARTICLE

Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens

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Aims To assess the tolerability of initiating/uptitrating sacubitril/valsartan (LCZ696) from 50 to 200 mg twice daily (target dose) over 3 and 6 weeks in heart failure (HF) patients (ejection fraction ≤35%).

Methods and results A 5-day open-label run-in (sacubitril/valsartan 50 mg twice daily) preceded an 11-week, double-blind, randomization period [100 mg twice daily for 2 weeks followed by 200 mg twice daily ('condensed' regimen) vs. 50 mg twice daily for 2 weeks, 100 mg twice daily for 3 weeks, followed by 200 mg twice daily ('conservative' regimen)]. Patients were stratified by pre-study dose of angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker (ACEI/ARB; low-dose stratum included ACEI/ARB-naïve patients). Of 540 patients entering run-in, 498 (92%) were randomized and 429 (86.1% of randomized) completed the study. Pre-defined tolerability criteria were hypotension, renal dysfunction and hyperkalaemia; and adjudicated angioedema, which occurred in ('condensed' vs. 'conservative') 9.7% vs. 8.4% ($P = 0.570$), 7.3% vs. 7.6% ($P = 0.990$), 7.7% vs. 4.4% ($P = 0.114$), and 0.0% vs. 0.8% of patients, respectively. Corresponding proportions for pre-defined systolic blood pressure <95 mmHg, serum potassium >5.5 mmol/L, and serum creatinine >3.0 mg/dL were 8.9% vs. 5.2% ($P = 0.102$), 7.3% vs. 4.0% ($P = 0.097$), and 0.4% vs. 0%, respectively. In total, 378 (76%) patients achieved and maintained sacubitril/valsartan 200 mg twice daily without dose interruption/down-titration over 12 weeks (77.8% vs. 84.3%

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for 'condensed' vs. 'conservative'; $P = 0.078$). Rates by ACEI/ARB pre-study dose stratification were 82.6% vs. 83.8% ($P = 0.783$) for high-dose/'condensed' vs. high-dose/'conservative' and 84.9% vs. 73.6% ($P = 0.030$) for low-dose/'conservative' vs. low-dose/'condensed'.

Conclusions Initiation/uptitration of sacubitril/valsartan from 50 to 200 mg twice daily over 3 or 6 weeks had a tolerability profile in line with other HF treatments. More gradual initiation/uptitration maximized attainment of target dose in the low-dose ACEI/ARB group.

Keywords LCZ696 • Sacubitril • Valsartan • ARNI • Heart failure • Tolerability

Introduction

The Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with angiotensin-converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial established the safety and tolerability of the target dose of the ARNI sacubitril/valsartan (200 mg twice daily), also known as LCZ696, in ambulatory patients with chronic heart failure with reduced ejection fraction (HFrEF) already treated with an ACEI/angiotensin receptor blocker (ARB). The trial included a single-blind active run-in period, during which tolerability to both enalapril and sacubitril/valsartan was assured prior to randomisation.[1,2] During the PARADIGM-HF run-in, patients transitioned from enalapril 10 mg twice daily to sacubitril/valsartan 100 mg (sacubitril 49 mg and valsartan 51 mg) twice daily and then sacubitril/valsartan 200 mg (sacubitril 97 mg and valsartan 103 mg) twice daily over a 6–8 week period before randomisation.

While the PARADIGM-HF population comprised patients pre-exposed to optimal doses of enalapril, it is accepted that many HFrEF patients encountered in routine practice are not at target doses of ACEI/ARBs.[3] The present trial addresses whether the tolerability of initiating sacubitril/valsartan is affected by the duration of the initiation/uptitration regimen. The rate of pre-specified adverse events associated with initiating/uptitrating sacubitril/valsartan using a short (3-week 'condensed') and longer (6-week 'conservative') duration was assessed in a broader range of patients than previously studied, including, hospitalized as well as ambulatory patients, and those treated with a low dose of ACEI/ARB or ACEI/ARB-naïve. Furthermore, patients were not required to have elevated levels of brain natriuretic peptide (BNP) or *N*-terminal pro-brain natriuretic peptide (NT-proBNP) before entry to the study. Therefore, TITRATION aimed to characterize the tolerability of initiating/uptitrating sacubitril/valsartan (LCZ696) in a range of patients representative of daily clinical practice, including patients naïve to or with varying levels of pre-exposure to ACEI/ARBs, using a 'condensed' and 'conservative' regimen.

Methods

Patients

Inpatient and outpatient males and females (≥18 years old) with heart failure (HF) [New York Heart Association (NYHA) functional class II–IV] with a reduced left ventricular ejection fraction (LVEF ≤35%) were potentially eligible for inclusion. One or more of the following additional eligibility requirements were required at screening: for outpatients currently treated with ACEI/ARB, the dose must have been stable for at least 2 weeks; to be classed as ACEI/ARB-naïve, the patient must not have taken ACEI/ARB for at least 4 weeks; hospitalized patients had to be either ACEI/ARB-naïve, or on a tolerated dose of an ACEI/ARB at screening. Elevated levels of BNP or NT-proBNP was not a requirement for participation in the study.

Other therapies representing optimal treatment under current guidelines,[4,5] including a β-blocker, mineralocorticoid receptor antagonist (MRA), cardiac resynchronization therapy and an implantable cardioverter–defibrillator were recommended in the protocol.

Key exclusion criteria included: previous intolerance to recommended target doses of ACEI/ARBs; symptomatic hypotension and/or a systolic blood pressure (SBP) <100 mmHg or SBP >180 mmHg at screening; estimated glomerular filtration rate (eGFR) < 30 mL/min.1.73 m^2 at screening; known history of angioedema; and current hospitalization for conditions other than decompensated HF.

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[6] and the Declaration of Helsinki.[7] The protocol was approved by each site's ethics committee; all patients gave written informed consent.

Study design and randomization

This multicentre, randomized, double-blind, parallel-group study comprised three phases: (i) a 1-week screening phase; (ii) a sacubitril/valsartan run-in phase lasting approximately 1 week (Day 1–5); and (iii) a randomized phase lasting approximately 11 weeks (*Figure 1*).

As both treatment arms start with sacubitril/valsartan 50 mg (sacubitril 24 mg and valsartan 26 mg) twice daily, the run-in phase was open-label to simplify the study. Patients were then randomized to one of the two blinded treatment arms. The 'condensed' uptitration arm comprised uptitration of sacubitril/valsartan from 50 mg twice daily to 200 mg twice daily over 3 weeks (including the run-in phase). The 'conservative' uptitration arm comprised uptitration of sacubitril/valsartan from 50 mg twice daily to 200 mg twice daily over 6 weeks (including the run-in phase). A double-dummy design was used to preserve blinding.

Patients were stratified according to dose of ACEI/ARB at screening, pre-specified as follows. 'High-dose' received a total daily dose >160 mg of valsartan or >10 mg of enalapril, or equivalent doses of other ARBs or ACEIs, respectively; 'low-dose' received a total daily dose ≤160 mg of valsartan or ≤10 mg of enalapril, or equivalent doses of other ARBs or ACEIs, respectively, at screening (see the

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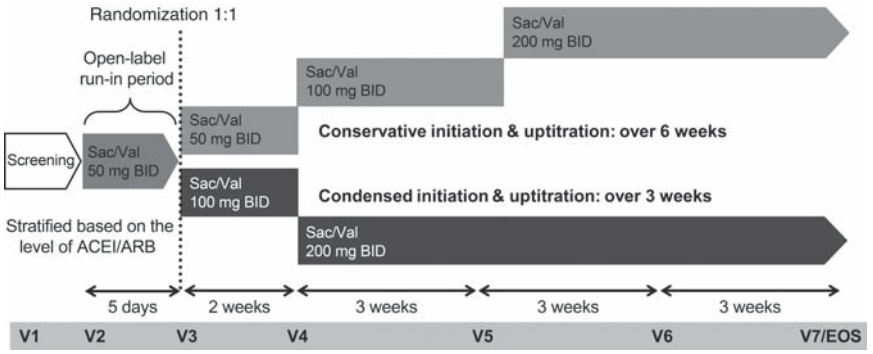

Figure 1 Study design. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BID, twice daily; EOS, end of study; Sac/Val, sacubitril/valsartan; V, visit.

Supplementary material online, *Table S1*). The 'low-dose' ACEI/ARB stratum also included patients who were ACEI/ARB-naïve.

Study procedures

All patients received open-label sacubitril/valsartan 50 mg twice daily during a 5-day run-in period. Patients using an ACEI before enrolment discontinued this treatment for a 36-h washout period before starting sacubitril/valsartan.

At the end of the run-in period, patients who were able to tolerate sacubitril/valsartan 50 mg twice daily according to the following criteria entered the double-blind, randomized phase: potassium level $\leq$5.4 mmol/L; an eGFR $\geq$30 mL/min.1.73 m^2 and eGFR reduction $\leq$35% compared with screening; no symptomatic hypotension and SBP $\geq$95 mmHg; no postural symptoms or any other adverse events (AEs) precluding continuation according to investigator judgment. Those not meeting these criteria were considered run-in failures.

Patients randomized to the 'condensed' uptitration arm were uptitrated to sacubitril/valsartan 100 mg twice daily for 2 weeks, followed by uptitration to sacubitril/valsartan 200 mg for the remaining study period. Patients randomized to the 'conservative' uptitration arm continued to receive sacubitril/valsartan 50 mg twice daily for 2 weeks followed by uptitration to sacubitril/valsartan 100 mg for further 3 weeks and to 200 mg twice daily thereafter until the end of study (*Figure 1*).

At each visit (*Figure 1*), the assessment of tolerability of sacubitril/valsartan was based on the tolerability criteria used for the run-in phase. Patients not meeting these criteria at any visit were considered treatment failures, as were those who required dose reduction/interruption in study medication. These patients were switched to open-label sacubitril/valsartan, the dose of which was at the discretion of the investigator.

Patients switched to open-label sacubitril/valsartan were uptitrated based on the investigator's judgment with the goal of achieving and maintaining sacubitril/valsartan 200 mg twice daily for at least the final 2 weeks leading to completion of the study.

Primary objective: tolerability according to predefined adverse events and laboratory assessments

The primary objective of the trial was to characterize the tolerability of the two initiation/uptitration regimens of sacubitril/valsartan in patients with HFrEF. The primary tolerability assessment was the number and proportion of patients in the two uptitration regimens who, following randomization, experienced pre-specified AEs coded according to the industry standard medical dictionary for regulatory activities (MedDRA).[8] These AEs were hypotension (MedDRA preferred terms: hypotension, orthostatic hypotension, or blood pressure decreased), hyperkalaemia (MedDRA preferred terms: hyperkalaemia or blood potassium increased), renal dysfunction (MedDRA preferred terms: blood creatinine increased, glomerular filtration rate decreased, renal failure, renal failure acute, renal failure chronic, or renal impairment), and angioedema (confirmed by the Angioedema Adjudication Committee).

Other pre-specified primary tolerability assessments included the number and proportion of patients experiencing SBP <95 mmHg or any of the following biochemical changes after randomization: serum potassium >5.5 mmol/L and $\geq$6.0 mmol/L, serum creatinine >3.0 mg/dL (267 µmol/L), and doubling of serum creatinine from baseline levels. These were all measured in a central laboratory (Eurofins Medinet LLC, Lancaster, PA, USA, for USA, and Eurofins Medinet BV, Breda, the Netherlands for non-USA).

Secondary objectives: proportion of patients achieving 'treatment success' or protocol-defined 'tolerability success'

The two secondary objectives were to assess: (i) 'treatment success' defined as the proportion of patients, excluding non-AE- or non-death-related discontinuations, in the two treatment groups who achieved and maintained a dose of sacubitril/valsartan 200 mg twice daily without any dose interruption or down-titration over 12 weeks; (ii) 'tolerability success' defined as the proportion of patients, excluding patients who discontinued for reasons other than AE or death, who tolerated a dose of sacubitril/valsartan of 200 mg twice daily for at least the final 2 weeks leading to study completion, regardless of previous dose interruption or down-titration.

Overall safety assessments comprised monitoring all AEs and serious AEs (SAEs), laboratory assessments, and vital signs, and are discussed in the Supplementary material online, *Appendix S2*.

Statistical analysis

TITRATION was not hypothesis driven as the primary objective was to characterize the tolerability of initiating sacubitril/valsartan using a 'conservative' and a 'condensed' uptitration regimen. Hence, the

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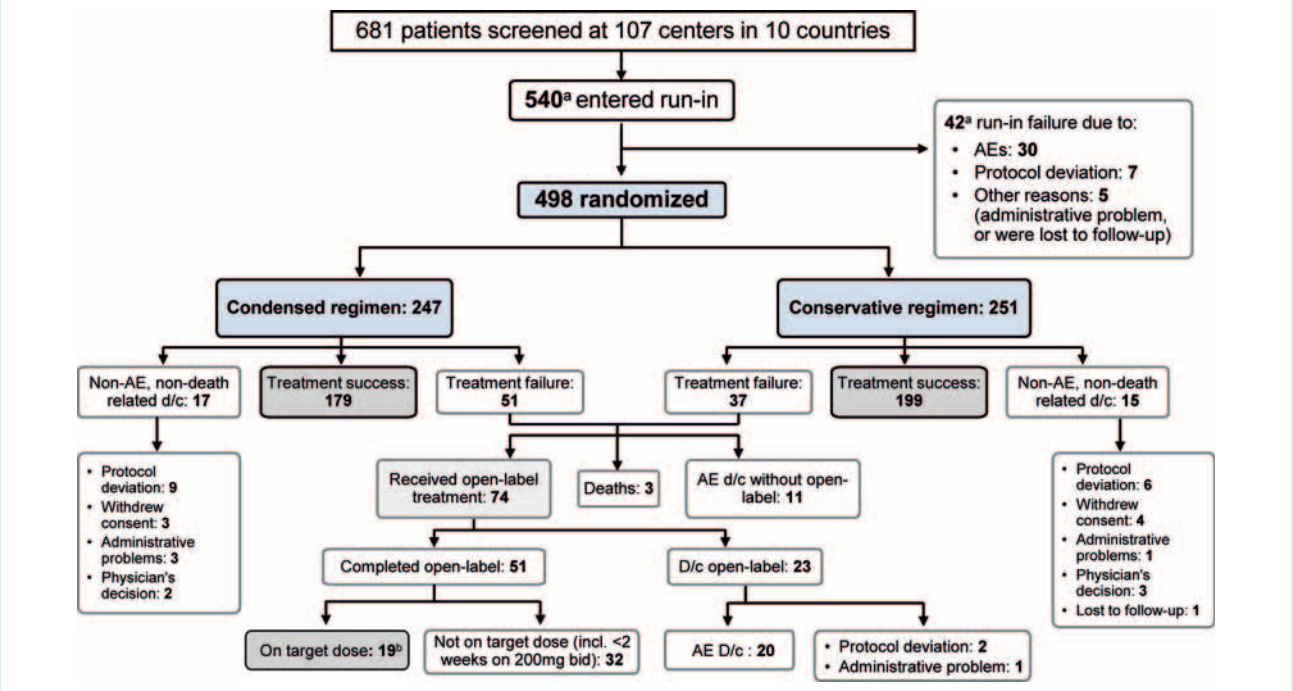

Figure 2 Patient disposition. [a]Includes two patients who discontinued run-in because of a protocol deviation without taking run-in medication; therefore, 538 patients received at least one dose of run-in medication. [b]Nineteen patients achieved target dose and maintained it for at least 2 weeks leading to study completion following dose interruption or down-titration, giving a total of 397 patients achieving 'tolerability success'. AE, adverse event; bid, twice daily; d/c, discontinuations.

sample size was not based on establishing the statistical significance of observed differences between uptitration regimens or stratum, but to provide precise estimates of the event rates in each stratum and uptitration regimen.

Assuming a 1:1 stratification between the high/low ACEI/ARB dose strata and based on the approximate event rates of 1.7%, 1.2%, 1.6%, and 0.1% for hypotension, hyperkalaemia, renal dysfunction, and angioedema, respectively, as estimated with available information from PARADIGM-HF at that time, a sample size of 120 per treatment per stratum (480 in total for both treatment arms) was expected to ensure adequate precision of the estimates [length of the 95% confidence interval (CI)] as 0.045, 0.038, 0.044, and 0.011, respectively. The primary analysis summarized descriptive statistics of count and percentage of the pre-specified adverse events and laboratory assessments throughout the double-blind treatment phase, within each stratum and each uptitration regimen.

For each of the events, the annualized percentage for the overall population was estimated using an exponential survival regression model, in which uptitration regimen and pre-study ACEI/ARB treatment level stratum (high/low) were fixed-effect factors. For stratum-specific estimates, separate exponential regression models with uptitration regimen as fixed effect factors were fitted. The annualized percentages were used to derive comparison between uptitration regimens within each stratum by estimating hazard ratios and their 95% CIs. Although *P*-values are presented, it is important to note that the study was not powered to detect statistically significant differences between regimens.

Secondary variables were analysed using a logistic regression model with uptitration regimen, pre-study ACEI/ARB treatment stratum, and region as fixed factors. For within-stratum-specific estimates, separate logistic regression models were fitted with uptitration regimen and region as the fixed factors. Statistical testing was performed at the two-sided significance level of 0.05 and estimated odds ratio and 95% CIs are provided.

Results

Study disposition

The study was carried out between November 2013 and August 2014. Patient disposition is summarized in *Figure 2*. Of 681 patients screened across 107 centres in 10 countries (for centres and principal investigators see the Supplementary material online, *Appendix S1*), 540 entered the run-in and 538 (99.6%) received at least one dose of sacubitril/valsartan 50 mg. Run-in failure occurred in 42 patients. Of the remaining 498 patients randomized, 429 (86.1%) patients completed the study while taking study medication (*Figure 2*). Reasons for study discontinuation during the run-in and after randomization are shown in the Supplementary material online, *Table S3*.

Patient characteristics

Baseline demographics and clinical characteristics, including medical history and treatment, were well balanced between the randomized groups (*Tables 1* and *2*). Most patients were ambulatory ($n = 56$, 11.2%, were inpatients) and male and were equally divided

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Table 1 Baseline demographics

Demographic	Titration regimen		ACEI/ARB dose stratum		Total ($n = 498$)
	Condensed ($n = 247$)	Conservative ($n = 251$)	High ($n = 247$)	Low ($n = 251$)	
Age (years)					
Mean (SD)	64.2 (11.86)	63.8 (10.94)	63.1 (12.10)	64.9 (10.60)	64.0 (11.39)
Gender, *n* (%)					
Male	191 (77.3)	201 (80.1)	196 (79.4)	196 (78.1)	392 (78.7)
Predominant race, *n* (%)					
Caucasian	228 (92.3)	234(93.2)	224 (90.7)	238 (94.8)	462 (92.8)
Black	12 (4.9)	11 (4.4)	12 (4.9)	11 (4.4)	23 (4.6)
Other	7 (2.8)	6 (2.4)	11 (4.5)	2 (0.8)	13 (2.6)
Patients composition, *n* (%)					
Inpatient	25 (10.1)	31 (12.4)	17 (6.9)	39 (15.5)	56 (11.2)
Outpatient	222 (89.9)	220 (87.6)	230 (93.1)	212 (84.5)	442 (88.8)
High-dose ACEI/ARB	120 (48.6)	127 (50.6)			247 (49.6)
Low-dose ACEI/ARB	127 (51.4)	124 (49.4)			251 (50.4)
ACEI/ARB-naïve*	17 (6.9)	16 (6.4)			33 (6.6)
Baseline LVEF (%)					
Mean (SD)	29.8 (5.15)	29.6 (5.36)	30.5 (5.08)	28.9 (5.32)	29.7 (5.25)
NYHA class at screening, *n* (%)					
II	175 (70.9)	178 (70.9)	191 (77.3)	162 (64.5)	353 (70.9)
III	72 (29.1)	72 (28.7)	56 (22.7)	88 (35.1)	144 (28.9)
IV	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.2)
Body mass index (kg/m^2) at screening					
Mean (SD)	30.9 (5.88)	30.6 (6.03)	31.6 (6.10)	30.0 (5.70)	30.8 (5.95)
SBP (mmHg) at Visit 2					
Mean (SD)	130.8 (16.64)	130.8 (15.98)	132.7 (16.91)	129.0 (15.49)	130.8 (16.30)
DBP (mmHg) at Visit 2					
Mean (SD)	77.2 (9.99)	77.6 (9.26)	78.0 (9.34)	76.8 (9.87)	77.4 (9.62)
Baseline eGFR (mL/min.1.73 m^2) at screening					
Mean (SD)	69.6 (21.63)	70.6 (25.16)	71.4 (21.85)	68.8 (24.90)	70.1 (23.45)
Baseline eGFR group (mL/min.1.73 m^2) at screening, *n* (%)					
<60	83 (33.6)	85 (33.9)	73 (29.6)	95 (37.8)	168 (33.7)
≥60	163 (66.0)	164 (65.3)	173 (70.0)	154 (61.4)	327 (65.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.
*Included in the overall low-dose ACEI/ARB stratum.

Table 2 Relevant medical history

	Sacubitril/valsartan Condensed ($n = 247$)	Sacubitril/valsartan Conservative ($n = 251$)	Total ($n = 498$)
Previous hospitalization because of heart failure at baseline	131 (53.0)	146 (58.2)	277 (55.6)
Treated with			
ACEI	170 (68.8)	161 (64.1)	331 (66.5)
ARB	60 (24.3)	74 (29.5)	134 (26.9)
Diuretic	205 (83.0)	195 (77.7)	400 (80.3)
Aldosterone antagonist	147 (59.5)	152 (60.6)	299 (60.0)
Beta-blocker	235 (95.1)	238 (94.8)	473 (95.0)
Cardiac resynchronization therapy	5 (2.0)	9 (3.6)	14 (2.8)
Implantable defibrillator insertion	44 (17.8)	37 (14.7)	81 (16.3)
Type 2 diabetes	31 (12.6)	30 (12.0)	61 (12.2)

Values are number (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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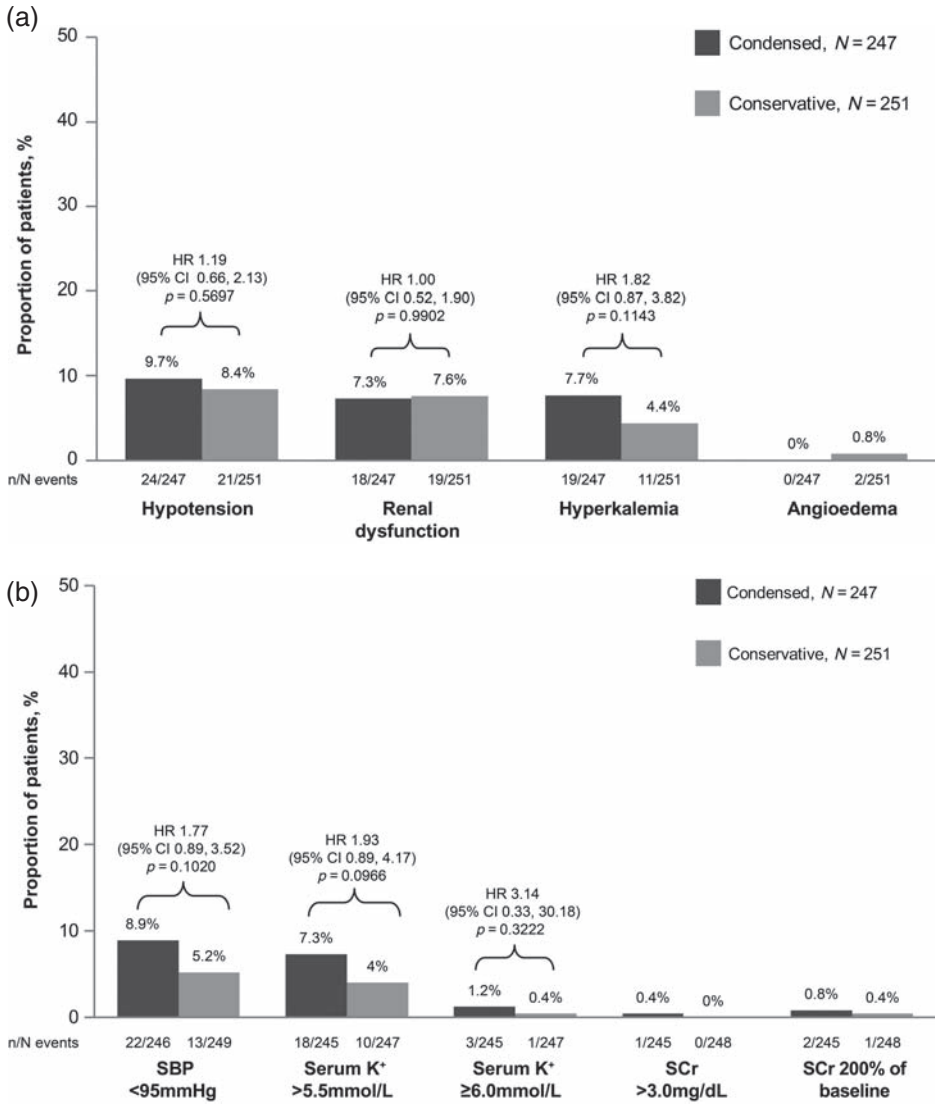

Figure 3 Primary endpoints by regimen. (a) Incidence of predefined adverse events. (b) Incidence of systolic blood pressure (SBP) <95 mmHg and pre-specified laboratory assessments. CI, confidence interval; HR, hazard ratio; SCr, serum creatinine.

between the low- and high-dose ACEI/ARB strata; 33 (6.6%) patients were ACEI/ARB-naïve. Approximately one-third had evidence of chronic kidney disease (eGFR <60 mL/min.1.73 m^2) and 12% had type 2 diabetes; approximately 60% were treated with a MRA and 95% with a beta-blocker.

Tolerability according to predefined adverse events

'Condensed' and 'conservative' initiation/uptitration regimens

As shown in *Figure 3* and *Table 3*, the incidence of hypotension was 9.7% vs. 8.4% in the 'condensed' and 'conservative' initiation/uptitration regimens, respectively, and for renal dysfunction 7.3% vs. 7.6%. The incidence of hyperkalaemia was 7.7% in the 'condensed' regimen and 4.4% in the 'conservative' regimen (*Figure 3* and *Table 3*). Angioedema was rare, with no cases in the 'condensed' uptitration group and two non-severe cases in the 'conservative' uptitration group (one of the two cases was reassessed by the Angioedema Adjudication Committee as 'not an angioedema event' after the database lock).

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker dose strata

Hypotension, renal dysfunction, and hyperkalaemia were each more common in the low-dose ACEI/ARB stratum, irrespective of uptitration regimen. The highest rate of these AEs was observed in the low-dose ACEI/ARB-'condensed' uptitration group (*Table 3*). In the high-dose ACEI/ARB stratum, rates of hypotension and

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Table 3 Primary and key secondary endpoints

Response variable	ACEI/ARB dose stratum	Sacubitril/valsartan Condensed *n/N* (%)	Sacubitril/valsartan Conservative *n/N* (%)	*P*-value
Pre-specified adverse events during post-randomization period				
Hypotension	High	5/120 (4.2)	7/127 (5.5)	0.657
	Low	19/127 (15.0)	14/124 (11.3)	0.353
	All	24/247 (9.7)	21/251 (8.4)	0.570
Renal dysfunction	High	5/120 (4.2)	9/127 (7.1)	0.371
	Low	13/127 (10.2)	10/124 (8.1)	0.492
	All	18/247 (7.3)	19/251 (7.6)	0.990
Hyperkalaemia	High	8/120 (6.7)	5/127 (3.9)	0.312
	Low	11/127 (8.7)	6/124 (4.8)	0.225
	All	19/247 (7.7)	11/251 (4.4)	0.114
Angioedema	High	0/120 (0.0)	1/127 (0.8)	–
	Low	0/127 (0.0)	1/124 (0.8)	–
	All	0/247 (0.0)	2*/251 (0.8)	–
Pre-specified abnormal central laboratory and vital signs outcomes during post-randomisation period				
SBP <95 mmHg	High	4/120 (3.3)	7/126 (5.6)	0.439
	Low	18/126 (14.3)	6/123 (4.9)	0.016
	All	22/246 (8.9)	13/249 (5.2)	0.102
Serum potassium >5.5 mmol/L				
	High	9/119 (7.6)	6/125 (4.8)	0.327
	Low	9/126 (7.1)	4/122 (3.3)	0.169
	All	18/245 (7.3)	10/247 (4.0)	0.097
Serum potassium ≥6.0 mmol/L	High	2/119 (1.7)	0/125 (0.0)	–
	Low	1/126 (0.8)	1/122 (0.8)	0.999
	All	3/245 (1.2)	1/247 (0.4)	0.322
Serum creatinine >3.0 mg/dL (267 μmol/L)	High	0/119 (0.0)	0/125 (0.0)	–
	Low	1/126 (0.8)	0/123 (0.0)	–
	All	1/245 (0.4)	0/248 (0.0)	–
Serum creatinine 200% of baseline	High	0/119 (0.0)	0/125 (0.0)	–
	Low	2/126 (1.6)	1/123 (0.8)	0.569
	All	2/245 (0.8)	1/248 (0.4)	–
Pre-specified 'treatment success' and 'tolerability success'		Sacubitril/valsartan Condensed, *n/N*† (%)	Sacubitril/valsartan Conservative, *n/N*† (%)	Odds ratio (95% CI)	
Treatment success	High	90/109 (82.6)	98/117 (83.8)	0.91 (0.45, 1.83)	0.783
	Low	89/121 (73.6)	101/119 (84.9)	0.50 (0.26, 0.94)	0.030
	All	179/230 (77.8)	199/236 (84.3)	0.65 (0.41, 1.05)	0.078
Tolerability success	High	94/109 (86.2)	103/117 (88.0)	0.84 (0.38, 1.84)	0.657
	Low	97/121 (80.2)	103/119 (86.6)	0.63 (0.32, 1.26)	0.189
	All	191/230 (83.0)	206/236 (87.3)	0.72 (0.43, 1.20)	0.207

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; n, total number of patients with specified adverse events included in the analysis; *N*, total number of patients included in the analysis; SBP, systolic blood pressure.
*One of the two cases in the post-randomization period was reassessed by the Angioedema Adjudication Committee as 'not an angioedema event' after the database lock.
†Excluding non-AE/death-related discontinuations.

renal dysfunction were similar in the two uptitration groups while hyperkalaemia was more frequent in the 'condensed' uptitration group. However, there was no apparent interaction between the ACEI/ARB dose stratum and uptitration regimen for any pre-defined AE (*Table 3*; see the Supplementary material online, *Table S2*).

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker-naïve patients

For ACEI/ARB-naïve patients, three episodes of hypotension were reported in each uptitration group ['condensed' uptitration group: 3 of 17 patients (17.6%); 'conservative' uptitration group: 3 of 16 patients (18.8%)]. The corresponding numbers for hyperkalaemia

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were 1 (6.0%) and 2 (12.5%), and for renal dysfunction they were 3 (17.6%) and 3 (18.8%). No angioedema AEs were reported for ACEI/ARB-naïve patients in either uptitration group. While the number of ACEI/ARB-naïve patients in the study was small, the rates of AEs were comparable to those observed for patients overall.

Tolerability according to predefined systolic blood pressure and laboratory thresholds

Results for the pre-specified SBP and laboratory measurement thresholds were in line with the pre-specified AEs (*Figure 3* and *Table 3*). The incidence of serum potassium >5.5 mmol/L was similar in the 'condensed' and 'conservative' uptitration regimen. There were few cases of serum potassium ≥6.0 mmol/L and few notable changes in serum creatinine (*Table 3*).

However, the incidence of SBP <95 mmHg in each of the ACEI/ARB strata differed according to uptitration regimen (interaction $P = 0.0392$; see the Supplementary material online, *Table S2*), driven by a difference in the rate of SBP <95 mmHg with the 'condensed' vs. 'conservative' uptitration regimens in the low-dose ACEI/ARB stratum (14.3% vs. 4.9%, $P = 0.016$) (*Table 3*).

The rates of SBP <95 mmHg in ACEI/ARB-naïve patients were similar to those in the low-dose ACEI/ARB stratum overall [2 of 17 patients (11.8%) and 2 of 16 patients (12.5%) for the 'condensed' and 'conservative' uptitration regimens, respectively].

Proportion of patients achieving pre-specified 'treatment success'

Overall, 378 of the 498 (75.9%) randomized patients achieved 'treatment success', defined as achieving and maintaining a dose of sacubitril/valsartan of 200 mg twice daily without any dose interruption/down-titration over 12 weeks. A total of 32 patients discontinued for reasons other than AE or death. When these patients were excluded ($n = 466$), the proportion achieving 'treatment success' was 81.1%.

When all patients taking run-in medication ($n = 538$) are considered, the proportion achieving treatment success was 70.3%. The corresponding rate was 76.2% when the 42 non-AE-related discontinuations are excluded from all patients taking run-in medication ($n = 496$).

'Condensed' and 'conservative' initiation/uptitration regimens

When analysed by uptitration regimen (excluding non-AE/non-death-related discontinuations, $n = 466$), treatment success was achieved in 77.8% of patients in the 'condensed' and 84.3% in the 'conservative' uptitration groups ($P = 0.078$; *Table 3*).

Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker dose strata

In the low-dose ACEI/ARB stratum, more patients in the 'conservative' uptitration group achieved treatment success compared with the 'condensed' uptitration group (84.9% vs. 73.6%, $P = 0.03$; Table *3*). In the high-dose ACEI/ARB stratum the uptitration regimen had no impact on the treatment success rate (corresponding rates of 83.8% and 82.6%, $P = 0.783$).

Patients switched to open-label sacubitril/valsartan after down-titration or dose interruption and proportion achieving 'tolerability success'

Of the 74 patients (15% of randomized patients) switched to open-label sacubitril/valsartan following down-titration/dose interruption during the post-randomization period, 19 (25.7%; 9 patients from the high-dose ACEI/ARB stratum and 10 patients from the low-dose ACEI/ARB stratum) were able to maintain a dose of sacubitril/valsartan 200 mg twice daily for at least the final 2 weeks leading to the completion of the study.

By definition, 'tolerability success' included all patients achieving 'treatment success' ($n = 378$) plus patients who achieved and maintained a dose of sacubitril/valsartan of 200 mg twice daily for at least the final 2 weeks leading to the completion of the study following down-titration/dose interruption and switch to open-label sacubitril/valsartan ($n = 19$). Therefore, the overall number of patients achieving tolerability success was 397 [85.2% of the randomized population, excluding non-AE/non-death discontinuations ($n = 466$) and 79.7% of all randomized patients ($n = 498$)].

The resulting proportion of patients achieving 'tolerability success' was comparable between 'condensed' and 'conservative' regimens (83.0% vs. 87.3%, $P = 0.207$) (*Table 3*).

Rates of achieving 'tolerability success' in the high-dose ACEI/ARB stratum were similar regardless of uptitration regimen (86.2% vs. 88.0%, $P = 0.656$). The 'tolerability success' rate in the low-dose ACEI/ARB stratum patients was higher with the 'conservative' compared with 'condensed' uptitration regimen (86.6% vs. 80.2%, $P = 0.189$).

'Treatment success' and 'tolerability success' rates in ACEI/ARB-naïve patients were generally comparable to the profile in the other low-dose ACEI/ARB stratum patients.

For further details on tolerability in patients switched to open-label sacubitril/valsartan after randomisation see the Supplementary material online, *Appendix S2*.

Discussion

Overall, the demography of the patients included in TITRATION was similar to other HF trials, including PARADIGM-HF, and to the European Society of Cardiology (ESC) long-term HF registry.[1,9,10] We found that rates of patients achieving and maintaining the target dose of sacubitril/valsartan of 200 mg twice daily exceeded 70% when all 498 randomized patients or all 538 patients receiving at least one dose of study medication were considered. Furthermore, 76% of patients achieved and maintained the target dose to the end of the 12-week study period when patients discontinuing for non-AE or non-death-related reasons were excluded.

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Hypotension and hyperkalaemia were the most commonly reported AEs, but most were not SAEs and did not lead to permanent discontinuation. There were two confirmed cases of angioedema overall [one in the run-in period (see the Supplementary material online, *Table S3*) and one in the post-randomization period]; neither case was serious or involved compromise of the airway.

Effect of uptitration regimen and pre-study exposure to angiotensin-converting enzyme inhibitor/angiotensin receptor blockers on the sacubitril/valsartan tolerability profile

We did not find a significant increase of pre-defined AEs (including hypotension, renal dysfunction and hyperkalaemia) and pre-defined SBP and laboratory thresholds with a more rapid uptitration; however, the numbers of events are small and need to be interpreted with caution. The tolerability profile of sacubitril/valsartan in TITRATION was within the range typically observed in other trials of approved HF therapies[1,11] even when initiating/uptitrating over 3 weeks. Therefore, the tolerability of initiating/uptitrating sacubitril/valsartan can be considered acceptable regardless of the uptitration regimen. However, according to pre-study dose of ACEI/ARB, more patients transitioned from a low ACEI/ARB dose or treatment-naïve patients were able to achieve and maintain the sacubitril/valsartan target dose if they were uptitrated more gradually. This difference was due to fewer hypotension, hyperkalaemia, and renal dysfunction-related AEs with uptitration over 6 weeks compared to 3 weeks. Conversely, approximately 84% of the patients pre-treated with a higher dose of ACEI/ARB achieved and maintained the target dose to the end of the 12-week study period regardless of the duration of sacubitril/valsartan uptitration. There were no notable differences between uptitration regimens in the proportion achieving and maintaining the target dose over the entire study period among hospitalized patients or among ACEI/ARB-naïve patients, although the number of patients in both subgroups was too small to draw reliable conclusions.

Achievement and maintenance of target dose in patients initially not tolerating sacubitril/valsartan

In patients not initially tolerating a dose of sacubitril/valsartan, the use of down-titration can result in the eventual achievement of the target dose. In fact, 26% of patients who had dose adjustment/interruption achieved the target dose for at least 2 weeks leading to the completion of the study. When taking these patients into account, >79% of the randomized population achieved and maintained sacubitril/valsartan 200 mg twice daily for at least the final 2 weeks of the study.

Clinical implications

The present study provides a practical approach to attaining the evidence-based dose of sacubitril/valsartan in a broad spectrum of patients with HFrEF. We have shown that with the more gradual 'conservative' uptitration regimen, a high rate of success is possible, even in patients taking a low dose (or naïve to) ACEI/ARB. Moreover, the high rates of successful uptitration were attained despite the addition of sacubitril/valsartan to other disease-modifying therapies including a β-blocker (in 95% of patients) and MRA (in 60%), which themselves reduce blood pressure and can cause renal dysfunction and hyperkalaemia.[4,5,12]

Limitations of the study

Limitations of the study included a number of exclusion criteria, notably hypotension and a low eGFR, and the small number of ACEI/ARB-naïve and hospitalized patients recruited. Indeed, there is a need for further study of the tolerability of sacubitril/valsartan in ACEI/ARB-naïve patients. In addition, while the regimen allocation was double-blind, the study was open-label in terms of the agent being received. Finally, the sample size was calculated to accurately characterize the tolerability of the 3- and 6-week initiation/uptitration regimens, but was not powered to detect differences in AE rates between regimens and strata.

Conclusions

In conclusion, we describe two initiation and uptitration regimens for sacubitril/valsartan, both of which had a tolerability profile considered in line with other treatments for HF. Notably, both regimens led to high rates of attainment of the target dose in a wide range of patients, including both inpatients and outpatients and those taking low doses of ACEI/ARB therapy. More gradual uptitration can increase the chance of attaining the target dose of sacubitril/valsartan in patients transitioning from lower doses of ACEI/ARBs.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Principal investigators (responsible for data collection).

Appendix S2. Tolerability in patients switched to open-label sacubitril/valsartan after randomization (treatment failures), study drug discontinuation and overall safety.

Table S1. Definition of low-dose and high-dose ACEI/ARB inhibition strata based on pre-study ACEI/ARB total daily dose at screening.

Table S2. Hazard rates and ratios for pre-specified AEs, SBP <95 mmHg, and laboratory criteria.

Table S3. Discontinuations for AEs during the run-in and post-randomization periods.

Table S4. Most common AEs (at least 2% in either uptitration group) in the post-randomized phase.

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Conflict of interest: M.S. reports consulting fees for Novartis and Abbott Vascular. J.J.V.M.s. employer, the University of Glasgow, was/is being paid by Novartis for his time spent as Executive Committee member/co-chair of PARADIGM-HF. R.W. has served as an investigator, consultant, or speaker for Bayer, CVRx, Boehringer Ingelheim, Johnson & Johnson, Medtronic, European Union, Bundesministerium für Bildung und Forschung, Novartis, Pfizer, Sanofi, and Servier. H.F.McI reports consulting fees for Novartis and Bayer. I.A. reports consulting fees for Novartis. M.B.Y. reports institutional fees from Novartis and Cardiorentis. I.M., J.N., M.R. and B.S., report study-related fees from Novartis. A.S., B.R., F.C. and A.C. are employees of Novartis. The remaining authors declare no conflicts of interest.

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