


Introduction of sacubitril/valsartan in primary care follow-up of heart failure: a prospective observational study (THESEUS)

Thomas Dieterle^{1,2*} , Stefan Schaefer^{3,4}, Ina Meyer⁵, Gabriele Ackermann⁵, Kashan Ahmed⁵ and Roger Hullin⁶

¹University Department of Medicine, Cantonal Hospital Baselland, Liestal, Switzerland; ²Faculty of Medicine, University of Basel, Basel, Switzerland; ³Arztpraxis Waltenschwil AG, Waltenschwil, Switzerland; ⁴Institute of Primary Care (IHAMZ), University and University Hospital of Zurich, Zurich, Switzerland; ⁵Novartis Pharma Switzerland AG, Rotkreuz, Switzerland; ⁶Cardiology, Cardiovascular Department, University Hospital Lausanne, University of Lausanne, Lausanne, Switzerland

Abstract

Aims Switch from angiotensin converting enzyme inhibitor treatment to sacubitril/valsartan (sac/val) is associated with benefit in heart failure with reduced ejection fraction (HFrEF). Reports on management of this switch are largely based on randomized controlled trials, retrospective analyses, and hospital-based care, while patients with chronic heart failure (CHF) are frequently followed-up in primary care. The THESEUS study aimed to characterize the transition to sac/val and early maintenance period of HFrEF in primary care.

Method and results THESEUS was a prospective, observational, non-interventional study, performed at primary care sites throughout Switzerland. Patient characteristics, sac/val transition, and maintenance were reported at study enrolment and approximately 3 and 6 months after sac/val initiation. The primary endpoint was achievement of 200 mg BID sac/val with maintenance for ≥ 12 weeks. Secondary outcomes included dosing regimens, healthcare utilization in the 6 months prior to sac/val initiation and during the study, patient well-being, safety, and tolerability. Fifty-eight patients with CHF were enrolled from 45 primary care centres. Six patients were excluded, and 19 achieved the primary endpoint (36.5%, Achievers). Non-Achievers underwent fewer titration steps than Achievers (1.9 ± 0.9 vs. 3.1 ± 1.4). In both groups, patient well-being improved and the percentage of New York Heart Association III patients decreased. Healthcare utilization decreased (19% vs. 30.8% in the 6 months pre-enrolment period). The most frequent reasons for target dose non-achievement were asymptomatic and symptomatic hypotension (15.3% and 12.1%, respectively).

Conclusions Results from THESEUS suggest that transition to sac/val is manageable in primary care, with a safety profile corresponding to reports from specialized heart failure care.

Keywords Heart failure; Disease management; Primary care

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*Correspondence to: Thomas Dieterle, MD, Klinik Arlesheim, Cardiology, Pfeffingerweg 1, CH-4144 Arlesheim, Switzerland.

Tel: +49 (0)172 7256798. Email: thomas.dieterle@unibas.ch

Introduction

Chronic heart failure (CHF) is associated with high mortality and morbidity and remains a burden to healthcare systems despite significant improvement in medical therapy.^{1–5} Sacubitril/valsartan (sac/val) is a first-in-class angiotensin receptor-neprilysin inhibitor indicated for patients with heart failure with reduced ejection fraction (HFrEF) who remain

symptomatic despite optimal therapy.^{5–8} In the PARADIGM-HF pivotal study, sac/val was superior to the angiotensin converting enzyme inhibitor (ACEI) enalapril for reducing risk of cardiovascular-related death and frequency of hospitalizations.⁹ As many patients with CHF are followed-up in primary care settings, it is important to establish how the PARADIGM-HF findings are translated into primary care practice and whether achievement of maximal

drug treatment compares with results from randomized controlled trials.^{9–13}

Hypotension, the most frequent sac/val-related adverse event (AE) in the PARADIGM-HF trial, can represent a barrier to initiating and up-titrating heart failure (HF) therapies to target doses.^{9–12} The TITRATION trial investigated the safety and tolerability of sac/val dosing strategies, finding sac/val to be well-tolerated regardless of up-titration regimen.¹³ In line with these studies, the recommended starting dose for sac/val is 100 mg BID followed by an increase at 2–4 weeks to 200 mg BID, while for patients not currently taking an ACEI or angiotensin receptor blocker (ARB), a starting dose of 50 mg BID with slow up-titration is recommended.^{6–8} It remains unknown whether these dosing recommendations are adopted in primary care, and how physician prescribing behaviour may be impacted by concerns such as hypotension.¹⁴

The present study aimed to characterize patients with chronic HFrEF in primary care who were considered for sac/val treatment and to describe challenges in achieving maximal sac/val treatment dose.

Methods

Study design and setting

THESEUS was a longitudinal, non-interventional, observational study in patients with chronic HFrEF in follow-up by primary care physicians in Switzerland. Besides the characterization of patients who were judged eligible for sac/val treatment, the primary objective was to assess the proportion of patients achieving the sac/val target dose of 200 mg BID with maintenance for ≥ 12 weeks (classified as 'Achievers'). Secondary objectives were to assess reasons for not achieving/maintaining the sac/val target dose, the safety and tolerability of sac/val, the number and duration of sac/val titration steps, reasons for discontinuation, use of replacement therapies, frequencies of healthcare utilization, concomitant HF treatment, treatment in the 6 month pre-baseline period, and relevant diagnostic procedures.

Data were collected prospectively starting with initiation of sac/val use and terminating at approximately 6 months thereafter. Study physicians were encouraged to follow the 2016 European Society of Cardiology guidelines for the management of HF whenever possible.⁵ However, the study did not impose any specific therapy protocol, diagnostic, or therapeutic procedures nor a predefined visit schedule. When available, data on echocardiographic left ventricular ejection fraction (LVEF) and laboratory data, such as serum creatinine or NT-proBNP, obtained during the study observation period were recorded. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula when serum

creatinine values were available.^{15,16} For all sites, study and safety training at the beginning of the study as well as regular monitoring, including source data verification, on a risk-based approach were performed by NOVARTIS®. The study protocol was approved by the Ethics Committee for Northwest and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz; EKNZ; BASEC ID 2016–00936). Written informed consent for study participation was given by all patients.

Inclusion/exclusion criteria

Primary care physician sites throughout Switzerland were eligible to participate. Patient inclusion criteria were age ≥ 18 years, HFrEF ($\leq 40\%$), New York Heart Association (NYHA) functional class II–IV, and either planned initiation of sac/val treatment or prior initiation < 3 months before enrolment. Exclusion criteria were acute decompensated HF requiring hospitalization at the point of screening/enrolment and concomitant or planned participation in any other clinical trial.

Study visits and data collection

Per protocol study visits were planned at the time of initiation of sac/val treatment or documentation of retrospective data if sac/val treatment had begun before enrolment (Visit 1, baseline), and at approximately 3 and 6 months (Visit 2, respectively, Visit 3) after patient enrolment. The exact interval lengths between visits were not stipulated by a predefined schedule in order to minimize interference with procedures of care established at the study centres.

Data collection ran August 2016–January 2018. Patient demographic characteristics and medical history were obtained from medical records. Data on dose titration, retention, and tolerability and safety were collected prospectively. Data on healthcare utilization were collected retrospectively for the 6 months prior to enrolment and prospectively thereafter. Visual analogue scale data on well-being were documented at every study visit. Concomitant or prior medications were coded using the World Health Organization Drug Reference List. Medical history, co-morbidities, AEs, and serious AEs were coded through version 21.0 of the Medical Dictionary for Regulatory Activities. Hypotension was classified as 'symptomatic' or 'asymptomatic' according to the study site investigator's judgement. Symptomatic hypotension was reported as AE. Source documents and patient identities were maintained by the study centres.

Statistical analysis

Based on the TITRATION trial, a cohort size of approximately 250 patients was targeted.¹³ However, despite extension of

the enrolment phase, this target was not met. Therefore, inferential statistics could not be applied, and all analyses remained descriptive. Validation of all data was performed according to a predefined plan. Final analyses were performed on enrolled patients who met the selection criteria and received at least one documented dose of sac/val. Observations compared 'Achievers' and 'Non-Achievers'. Statistical analysis was performed using IBM-SPSS Statistics Version 25 (IBM Switzerland, CH-8010 Zürich).

Results

Patient characteristics

Forty-five primary care centres throughout Switzerland were recruited. Eighteen centres were prematurely terminated because of non-recruitment of patients. Fifty-eight patients were enrolled from the remaining centres (one to six patients per centre). Six patients were excluded, and 52 retained in the final analyses; forty-three patients completed the study

to Visit 3 (Figure 1). Patient characteristics at baseline are given in Table 1. While almost all patients had received some previous CHF medication (92.3%), only 48.1%, respectively, 21.2% of patients had received an ACEI or an ARB (Table 1).

Sacubitril/valsartan dose titration

Nineteen of 52 patients (36.5%) achieved the primary endpoint of the recommended sac/val target dose of 200 mg BID with maintenance for ≥ 12 weeks ('Achievers'), 13/33 male patients (39.4%) and 6/19 female patients (31.6%). 'Achiever' rates were 37.5% in current smokers, 41.7% in former smokers, 34.5% in non-smokers, and 33.3% in patients with unknown smoking status.

Seventeen of 51 patients (nine 'Achievers' and eight 'Non-Achievers') were initiated with sac/val at the recommended dosage of 100 mg BID (Figure S2).⁶⁻⁹ Overall, patients underwent a median of two titration steps. The rate of patients who underwent ≤ 2 titration steps was 78.8% in 'Non-Achievers' (mean 1.9, range 1-4 steps) and 47.4% in 'Achievers' (mean 3.1, range 2-6 steps; Figure 2).

Figure 1 Study flow diagram.

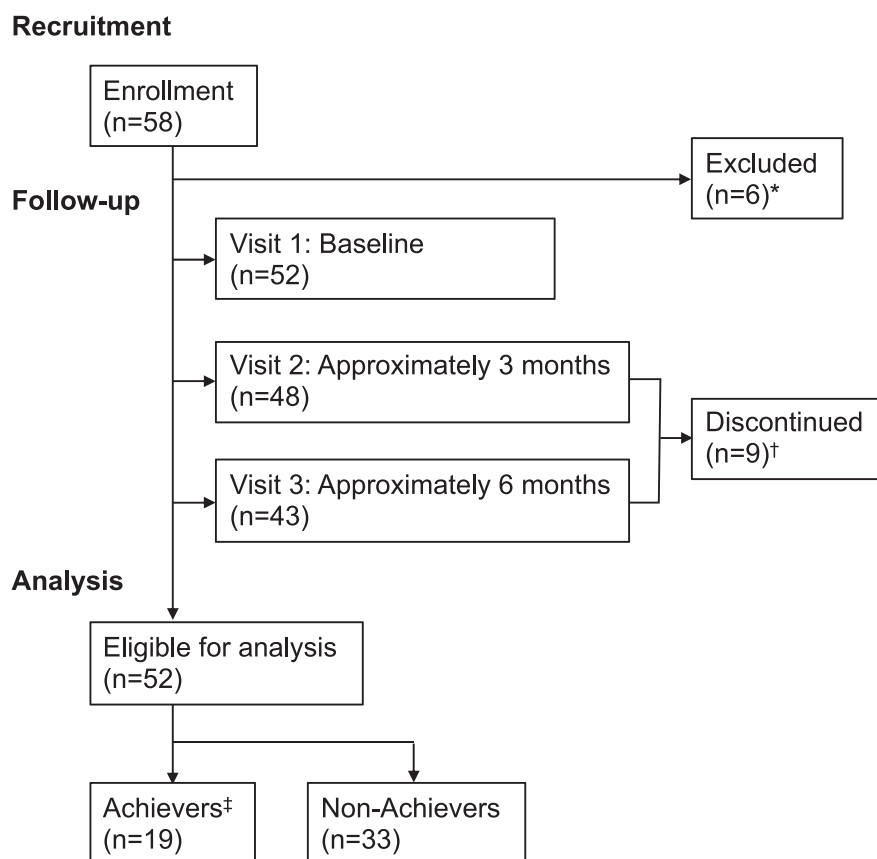


Table 1 Patient characteristics at baseline (Visit 1)

Characteristic		All patients (total <i>n</i> = 52)			
Age, median years (SD; range)		78.0 (10.7; 47–98)			
Sex, <i>n</i> female (%)		19 (36.5)			
BMI, median kg/m ² (range)		27.5 (16–44.6)			
Current smokers, <i>n</i> (%)		8 (15.4)			
Co-morbidities, ^a <i>n</i> (%)	Hypertension	29 (55.8)			
	Diabetes	17 (32.7)			
	Coronary artery disease	9 (17.3)			
	Atrial fibrillation	14 (26.9)			
	Hypercholesterolemia	13 (25.0)			
Duration of CHF with reduced ejection fraction, mean years (SD)		4.6 (5.8)			
NYHA class, <i>n</i> (%)	Class I	0			
	Class II	17 (32.7)			
	Class III	35 (67.3)			
	Class IV	0			
Prior treatment, ^{a,c} <i>n</i> (%)	Heart failure medication ^d	Any	48 (92.3)		
		ACE inhibitors ^e	25 (48.1)		
		ARBs ^f	11 (21.2)		
		Beta-blockers ^g	36 (69.2)		
		Diuretics	32 (61.5)		
		Ivabradine	1 (1.9)		
		MRAs	17 (32.7)		
		Other	2 (3.8)		
		Concomitant treatments, ^{a,h} <i>n</i> (%)	Non-heart failure medication ^d	Any	36 (69.2)
				ACE inhibitors ^e	49 (94.2)
ARBs ^f	3 (5.8)				
Beta-blockers ^g	38 (73.1)				
Diuretics	30 (57.7)				
Heart failure medication ^d	Ivabradine		0		
	MRAs		19 (36.5)		
	Other		2 (3.8)		
	Non-heart failure medication ^{b,d}		37 (71.2)		

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

^aMultiple coding entries per patient were possible. Patients with multiple entries within a coding level are counted only once.

^bIncludes stent placements and myocardial infarctions that were not documented as coronary artery disease.

^cTreatments started before initiation of sac/val treatment.

^dAccording to ESC guidelines.⁵

^eAlone or in combination with diuretics.

^fAlone or in combination with channel blockers or diuretics.

^gSelective.

^hTreatments started after or on initiation of sac/val treatment or ongoing during sac/val treatment.

Discontinuation of sac/val treatment occurred in 37.5% of 'Non-Achievers' and 5.3% of 'Achievers'.

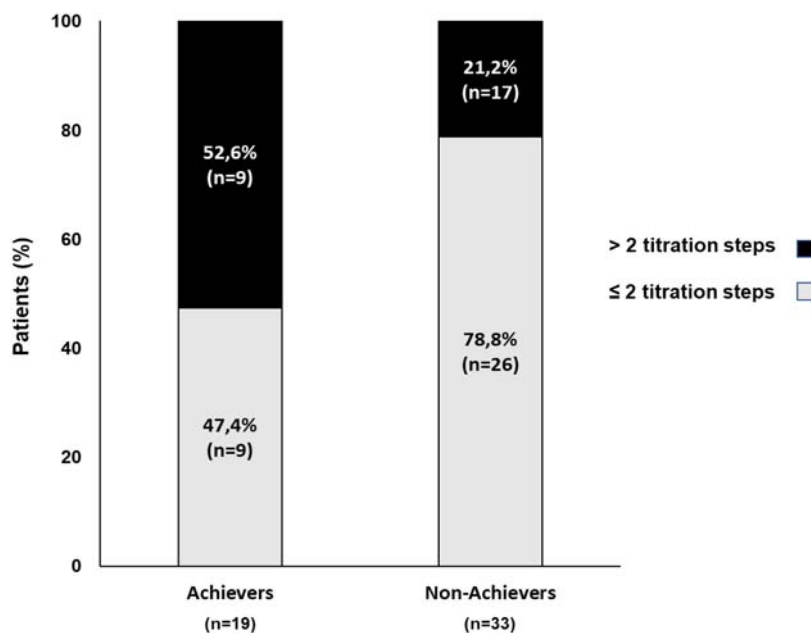
Reasons for not achieving the target dose

Table 2 provides the documented reasons for discontinuation, down-titration, or omission of up-titration for target dose in both 'Achievers' and 'Non-Achievers'. The most common reason observed in 'Non-Achievers' was asymptomatic, respectively, symptomatic hypotension (15.2%, respectively, 12.1% of patients). Other reasons among 'Non-Achievers' were increased serum creatinine, dose adaptation to renal function, hyperkalaemia, decision of the patient or the treating physician, or other AEs. Among 'Achievers', one case of symptomatic hypotension was observed.

Characteristics of target dose Achievers and Non-Achievers

In both 'Achievers' and 'Non-Achievers', the proportion of patients in NYHA class II increased while the proportion of patients in NYHA class III category decreased over time (Figure 3). Comparing Achievers with Non-Achievers at Visit 1, no significant differences were found for LVEF (35.0% vs. 35.0%, $P = 0.29$), serum creatinine (101.0 $\mu\text{mol/l}$ vs. 99.0 $\mu\text{mol/l}$, $P = 0.76$), or eGFR (64.0 mL/min vs. 53.1 mL/min, $P = 0.29$). In addition, no significant changes for eGFR were observed at Visit 3 compared with Visit 1 (Achievers: 64.0 mL/min vs. 55.2 mL/min, $P = 0.53$; Non-Achievers: 53.1 mL/min vs. 52.6 mL/min, $P = 0.62$). Assessment of visual analogue scale, by both patients and physicians, indicated an increase in well-being over the course of the study in the entire study population (Figure S1). Healthcare utilization frequencies

Figure 2 Proportion of Achievers and Non-Achievers undergoing ≤ 2 or > 2 titration steps. Achievers were defined as patients reaching the target dose of 200 mg BID sac/val with dose maintenance for ≥ 12 weeks.



Mean (SD)	3.1 (1.4)	1.9 (0.9)
Range	2 – 6	1 – 4

Table 2 Reasons for discontinuation, down-titration, or omission of up-titration

Reason given	Achievers (n = 19)	Non-Achievers (n = 33)	Total (n = 52)
Symptomatic, ^a n (%)	1 (5.3)	4 (12.1)	5 (9.6)
Asymptomatic hypotension, ^b n (%)	0	5 (15.2)	5 (9.6)
Increase in serum creatinine, n (%)	0	2 (6.1)	2 (3.8)
Hyperkalaemia, n (%)	0	1 (3.0)	1 (1.9)
Other AE, n (%)	0	2 (6.1)	2 (3.8)
Lack of compliance, n (%)	1 (5.3)	0	1 (1.9)
Patient's decision, n (%)	0	1 (3.0)	1 (1.9)
Other, ^c n (%)	1 (5.3)	5 (15.2)	6 (11.5)
Total ^d	2 (10.5)	13 (39.4)	15 (28.8)

Achievers were defined as patients reaching the target dose of 200 mg BID sac/val with dose maintenance for ≥ 12 weeks. AE, adverse event.

^aHypotension reported as an AE. Four of five cases were related to sac/val treatment.

^bHypotension not reported as an AE.

^cOther reasons included—for Achievers: pre-empting of possible hypotension that did not occur (one patient); for Non-Achievers: adaption to renal function (two patients), physician judgement (two patients), and cardiologist judgement (one patient).

^dMultiple entries possible per patient.

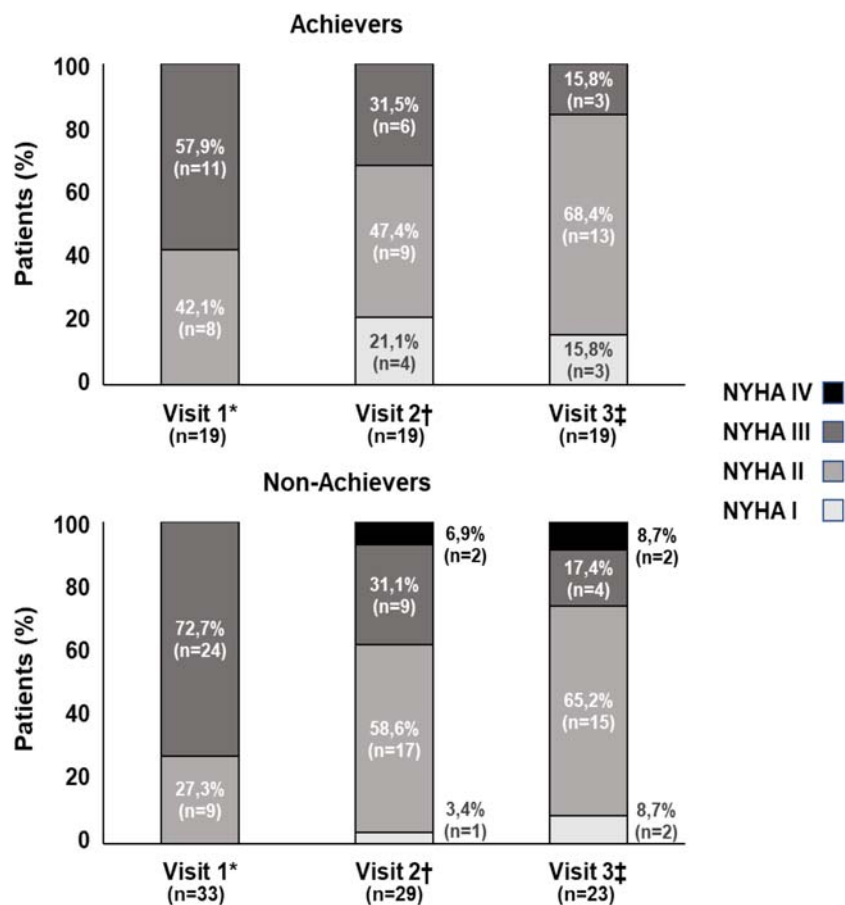
were lower during the study than the 6 months prior to baseline (Table S1). At Visit 3, 88.1% patients reported to intend to continue treatment.

Safety and tolerability

Twenty-eight AEs were reported in 13 patients, of which eight were considered sac/val related (Table 3). All treatment-related AEs were non-serious. Body weight remained constant, and blood pressure assessments did not indicate safety issues with sac/val. No clinically significant changes were observed for haemoglobin, sodium, potassium, creatinine, or urea levels (Table S2).

Discussion

In our study of sac/val use in primary care, the target sac/val dose of 200 mg BID with maintenance for ≥ 12 weeks was achieved in 36.5% of participants. The most important difference between primary endpoint 'Achievers' and 'Non-Achievers' in this out-of-hospital setting was the number of

Figure 3 New York Heart Association (NYHA) classification over time.

titration steps which were higher in the 'Achievers' group while the number of sac/val secondary effects was lower in this group.

Table 3 Frequency of adverse events

Adverse events	Number of patients, ^b n (%)	Number of events, n
Any	13 (25.0)	28
Serious, ^a	9 (17.3)	12
Treatment-emergent		
Hyperkalaemia	1 (1.9)	1
Dizziness	1 (1.9)	1
Generalized pruritus	1 (1.9)	1
Urticaria	1 (1.9)	1
Hypotension	4 (7.7)	4
Total	6 (11.5)	8
Treatment-emergent, serious	0	0
Total number of patients	52	NA

AE, adverse event; SAE, serious adverse event.

^aSAEs were cardiac failure (three patients), traumatic fracture (one patient), bladder transitional cell carcinoma (one patient), metastasis (one patient), pancreatic neoplasm (one patient), cerebellar ischemia (one patient), syncope (one patient), acute kidney injury (one patient), renal failure (one patient), and hypotension (one patient).

^bMore than one AE may have been reported in the same patient.

The low rate of sac/val target dose achievement is in line with previous reports from CHF outpatient clinics.^{17,18} Nevertheless, NYHA classification and well-being improved for both 'Achievers' and 'Non-Achievers', suggesting that patients had improved well-being and clinical stability compared with their pretrial experience regardless of sac/val target dose achievement or maintenance. In addition, when comparing with the 6 months period preceding the trial, less healthcare utilization was observed with sac/val treatment on both 'Achievers' and 'Non-Achievers', which is in accordance with a reduced number of unplanned rehospitalizations found in PARADIGM-HF.⁹

The most common documented reason for discontinuation, down-titration, or lack of up-titration in 'Non-Achievers' was hypotension. Only one case of hypotension was reported in the 'Achiever' group. Being in accordance with previous studies that reported hypotension as a key reason for sac/val discontinuation or lack of dose maintenance, this study points to a further factor, that is concerns for renal impairment with sac/val therapy, that may influence prescribing behaviour and represented a reason for endpoint non-achievement in two patients.^{14,19}

We further explored sac/val prescription patterns by reviewing the number of titration steps as a measure of dose escalation rate. Most 'Non-Achievers' underwent an average of ≤ 2 titration steps, while the majority of 'Achievers' followed a slower dose increase involving > 2 titration steps. These data suggest that in primary care, a slower approach to achieving the target dose, through multiple up-titration and down-titration of dose regimen, may be more successful than rapid up-titration. This corresponds to findings in the PARADIGM-HF and TITRATION studies in the setting of cardiologists' care.^{14,19}

Seventeen of the 51 patients in our study received a sac/val starting dose of 100 mg BID. According to the prescribing information, this is the recommended starting dose, unless a patient is currently not receiving an ACEI or ARB, in which case 50 mg BID is advised.^{6–8} In our study, 25 patients were prescribed this alternative regimen. In addition, eight patients received even lower starting doses (Figure S2).

While this —more conservative— choice of dosing regimens may reflect primary care practices observed for other HF medications, such as BBLs and ACEIs, it may also be attributed to the characteristics of the population included in THESEUS. Concomitant diseases found were typical for a chronic HFrEF population in Switzerland.²⁰ Compared with previous trials such as PARADIGM-HF, TITRATION, or TRANSITION, average patient age and the proportion of female patients were higher in THESEUS.^{9,13,21} Renal dysfunction, expressed as eGFR, at baseline was more pronounced than in the TITRATION and TRANSITION trials. Though LVEF in THESEUS was slightly higher at baseline and the prevalence of common risk factors such as hypertension and diabetes mellitus were lower, the higher average NYHA class and more patients in NYHA class III suggested that patients in THESEUS were more symptomatic than in PARADIGM-HF, TITRATION, and TRANSITION.^{9,13,21}

Nineteen of 52 patients (36.5%) achieved the primary endpoint of the recommended sac/val target dose of 200 mg BID with maintenance for ≥ 12 weeks. Successful titration to target dose was substantially lower compared with previous studies reporting patient rates achieving the recommended target dose in the range of 65% to about 83%.^{13,21–23} The rate of patients maintaining a dose of sac/val of 200 mg BID for longer periods was reported to be 65%. Taken together, these rates are substantially higher than in the THESEUS study.

Current guidelines for the management of HF recommend switching to sac/val in case of progression of HF, respectively, persistent signs and symptoms of HF despite optimal standard treatment.⁵ Given the higher age together with more pronounced, potentially age-related, co-morbidities, such as renal dysfunction in the patients included in THESEUS, the lower rate of patients achieving, respectively, maintaining the target dose compared with previous trials appears to be

related to increased morbidity as well as apparently more advanced HFrEF disease.

Almost all patients had received some kind of CHF medication prior to study inclusion. Interestingly, pretrial use of ACEIs, ARBs, diuretics, BBLs, and MRAs in THESEUS was lower compared with PARADIGM-HF.^{5,9} Furthermore, considering that sac/val is a second-line recommendation following treatment with an ACEI or ARB, we noted that only 48.1%, respectively, 21.2% of patients had previously received these medications.⁵ Of note, three patients continued on ACEIs despite the fact that co-medication of sac/val and an ACEI is contraindicated.

From a cardiologist's perspective, this lack of adherence to guidelines is notable but corresponds with reports of guideline implementation in routine practice being suboptimal, albeit improving.^{24,25} Reasons for guideline deviations may include ACEI and ARB intolerance, unawareness of prior treatments, and misinformation surrounding the mechanism and effects of sac/val but may also be a reflection of the complexity of HF management and unawareness of the treatment algorithm in HFrEF.

Strengths and limitations

To our knowledge, this is the first prospective, non-interventional trial documenting the behaviour of physicians prescribing sac/val in primary care. The study did not stipulate treatments, procedures, tests, or visit schedules, which by itself can introduce variability and unexpected findings because of the absence of a strict study protocol. As low recruitment precluded statistical comparisons, the data remain descriptive. Nevertheless, this study uncovered obstacles that may influence sac/val prescription and the management of CHF in primary care. Furthermore, although physicians were advised to recruit all eligible patient and ideally consecutive patients in order to reduce reporting and selection biases, we cannot exclude willingness to recruit, as suggested by the variation of recruited patients per study centre, as a confounder.

Conclusions

The prospective, observational THESEUS trial provides valuable insight into the challenges associated with the management and the prescription of sac/val in primary care. Only 36.5% of patients reached the recommended target dose of 200 mg BID sac/val with maintenance for ≥ 12 weeks. 'Achievers' and 'Non-Achievers' both showed improvement in well-being, clinical characteristics, and reduction in healthcare utilization during study participation, suggesting that benefit may not be limited to the maximal study drug dose alone. The safety analysis demonstrated that sac/val-

related AEs were considered to be non-serious. Clinical and laboratory parameters did not indicate any safety issues.

Data from the THESEUS study indicate that, in the large majority of cases treatment with an angiotensin receptor-neprilysin inhibitor may be handled by physicians in primary care without the need for referral to the specialist. However, the experience from the THESEUS study also indicates that several factors may be of importance in order to achieve and maintain maximal doses of sac/val in HFREF patients. Among those, close monitoring of blood pressure and avoiding low blood pressures at the time of initiation and during up-titration of sac/val treatment, careful up-titration of sac/val using lower dose increases, and a higher number of titration steps than currently recommended by guidelines, in particular in older patients with co-morbidities such as renal dysfunction, appear to be important measures that help to successfully initiate, up-titrate, and maintain sac/val therapy in patients with HFREF.

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Conflict of interest

The THESEUS trial was funded by Novartis Pharma Switzerland. GKM Gesellschaft für Therapieforchung supported in the design and implementation of the study. Thomas Dieterle has received honoraria from Novartis Pharma Switzerland for presenting at THESEUS investigator meetings (paid to the research fund of University Department of Medicine, Cantonal Hospital Baselland). Stefan Schäfer has been previously employed by, received honoraria from, or provided consultancy for several companies including AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Sanofi, Synthon, and Vifor Pharma. Ina Meyer, Gabriele Ackermann, and Kashan Ahmed are employed by Novartis Pharma Switzerland.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Patient well-being over time.

Figure S2. Frequencies of dosing regimens at first and last titration step.

Table S1. Frequencies of healthcare utilisation.

Table S2. Clinical and laboratory assessments over time.

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