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ORIGINAL PAPER

Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction

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Abstract

Background Sacubitril/valsartan reduced the occurrence of sudden cardiac death in the PARADIGM-HF trial. However, limited information is available about the mechanism.

Methods Heart failure (HF)-patients receiving sacubitril/valsartan for a class-I indication equipped with an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) with remote tele-monitoring were retrospectively analyzed. Device-registered arrhythmic-events were determined [ventricular tachycardia/fibrillation (VT/VF), appropriate therapy, non-sustained VT (NsVT; > 4beats and < 30 s), hourly premature ventricular contraction (PVC)-burden], following sacubitril/valsartan initiation (incident-analysis) and over an equal time period before initiation (antecedent-analysis). Reverse remodeling to sacubitril/valsartan was defined as an improvement of left ventricular ejection fraction of ≥ 5% between baseline and follow-up.

Results A-total of 151 HF-patients with reduced LVEF (29 ± 9%) were included. Patients were switched from ACE-I or ARB to equal doses of sacubitril/valsartan (expressed as %-target-dose; before = 58 ± 30% vs. after = 56 ± 27%). The mean follow-up of both the incident and antecedent analysis was 364 days. Following the initiation, VT/VF-burden dropped (individual patients with VT/VF pre_n = 19 vs. post_n = 10, total-episodes of VT/VF pre_n = 51 vs. post_n = 14, both $p < 0.001$), resulting in reduced occurrence of appropriate therapy (pre_n = 16 vs. post_n = 6; $p < 0.001$). NsVT-burden per patient also dropped (mean episodes pre_n = 7.7 ± 11.8 vs. post_n = 3.7 ± 5.4; $p < 0.001$). There was no impact on atrial-fibrillation burden. PVC-burden dropped significantly which was associated with an improvement in BiV-pacing in patients with < 90% BiV-pacing at baseline. A higher degree of reverse remodeling was associated with a lower burden of NsVT and PVCs (both $p < 0.05$).

Conclusion Initiation of sacubitril/valsartan is associated with a lower degree of VT/VF, resulting in less ICD-interventions. This beneficial effect on ventricular arrhythmias might be related to cardiac reverse remodeling.

Keywords Sacubitril/valsartan · Pharmacology · Heart failure · Ventricular arrhythmias · Reverse remodeling

Introduction

Background therapy with different classes of neurohormonal blockers has significantly reduced the risk of dying from sudden cardiac death (SCD) in patients with heart failure and reduced ejection fraction over the past 2 decades [1]. More recently, sacubitril/valsartan therapy reduced the risk of SCD in the "Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial", in comparison to guideline-recommended doses of enalapril [2]. Nevertheless, the definition of SCD in clinical

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trials is often vague and arbitrarily defined (unexpected death within 1 h after acute symptom onset if witnessed, or within 24 h if unwitnessed or after resuscitation for cardiac arrest); adjudicated by a board based on limited information and does not give information about the underlying mechanism [3]. Indeed, a pleiotropy of events other than ventricular tachyarrhythmias can lead to sudden death. For instance, an autopsy-controlled evaluation of patients with implantable cardiac devices dying from clinically defined sudden cardiac death, illustrated that only up to 2/3 had device-registered events [4]. Furthermore, in the American national registry of wearable cardioverter defibrillators, more than 20% of SCD were not related to ventricular arrhythmias [5]. Moreover, the recent DANISH-trial (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) underscores the importance of disease-modifying therapies in modulating the risk of SCD and the potential impact on allocation of primary prevention implantable cardioverter defibrillators (ICD) [6]. Therefore, knowing the ventricular arrhythmia prevalence in relation to sacubitril/valsartan initiation is of clinical interest.

Methods

Study population

All patients receiving therapy with sacubitril/valsartan in a single tertiary heart failure clinic (ZOL Genk, Belgium) between December 2016 and January 2018 were identified using the electronic health record. Inclusion criteria for the current analysis included; (A) an indication for sacubitril/valsartan according to Belgian reimbursement criteria; (1) symptomatic heart failure defined as New York Heart Association (NYHA) class II–IV, (2) left ventricular ejection fraction (LVEF) below 35% measured by echocardiography, (3) pretreatment with an individual optimal dose of angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB). And (B) the presence of an ICD or cardiac resynchronization therapy (CRT), followed through a remote tele-monitoring program. To be included for the analysis, the ICD or CRT had to be implanted at least 6 months prior to initiation of sacubitril/valsartan and the pre-exposure time in comparison to the post-exposure time to sacubitril/valsartan therapy while being in remote tele-monitoring had to be equal or more. The indications for CRT and ICD were in accordance to ESC-guidelines [7]. The choice between CRT-Pacemaker vs. CRT-defibrillator has been published previously [8]. The anti-tachy programming of ICDs throughout the study follow-up was based upon the primary vs. secondary prevention indication, and was left at the discretion of the treating physician. However, especially in primary prevention ICDs, there was a focus on low-rate detection zone (160 bpm) with therapy zones utilizing higher rates and delayed detection [9].

Collection of baseline characteristics

The electronic health record was used to retrospectively collect all baseline data from the moment that sacubitril/valsartan was initiated. We retrospectively collected baseline demographics, physical features, etiology of heart failure, presence of comorbidities, NYHA class at initiation of therapy, baseline laboratory, electrocardiogram features, transthoracic echocardiogram features and baseline medical and heart failure therapy. The dose of renin–angiotensin–aldosterone blockade was calculated as percent of target dose as published previously [10]. The final medical visit was used to determine the actual dose of sacubitril/valsartan and potential changes in anti-arrhythmic medications and other neurohormonal blockers, occurrence of therapies that could modulate the cardiac reserve remodeling or the risk of ventricular arrhythmias (VT, AF or AV-nodal-ablation, percutaneous coronary interventions, valve interventions). Additionally, the potassium values were checked at baseline and follow-up.

Remote tele-monitoring evaluation

ICDs and CRTs from four different vendors are implanted at our institution and all different vendors were included in the analysis. Periodic transmission is typically programmed on a monthly basis. For Medtronic devices remote tele-monitoring data were retrospectively accessed on the Carelink platform, for Boston Scientific devices the Latitude platform, St. Jude (Abbott) devices the Merlin-network and for Biotronik devices the Home Monitoring Service Center. The remote tele-monitoring platform was used to retrospectively collect the amount of ventricular arrhythmias, atrial arrhythmias and pacing features (see clinical endpoints). Remote tele-monitoring rapports were accessed between May and June 2018. Per individual patient, the exposure time to sacubitril/valsartan was calculated. For all patients, the pre-exposure time before initiation of sacubitril/valsartan was matched to correspond to a similar post-exposure time exposure after initiation of sacubitril/valsartan. Such antecedent/ incident analysis are well-validated methods to compare the occurrence of events before and after the initiation of a certain therapy, while using the patient as his own control [11]. Because the online tele-monitoring platforms differ for each vendor, different techniques were used to match the antecedent and incident timings (see Fig. 1). For Medtronic and St. Jude devices, all events were summed for individual blocks of 1 month. This technique was also used for Boston Scientific devices. However, for Boston Scientific

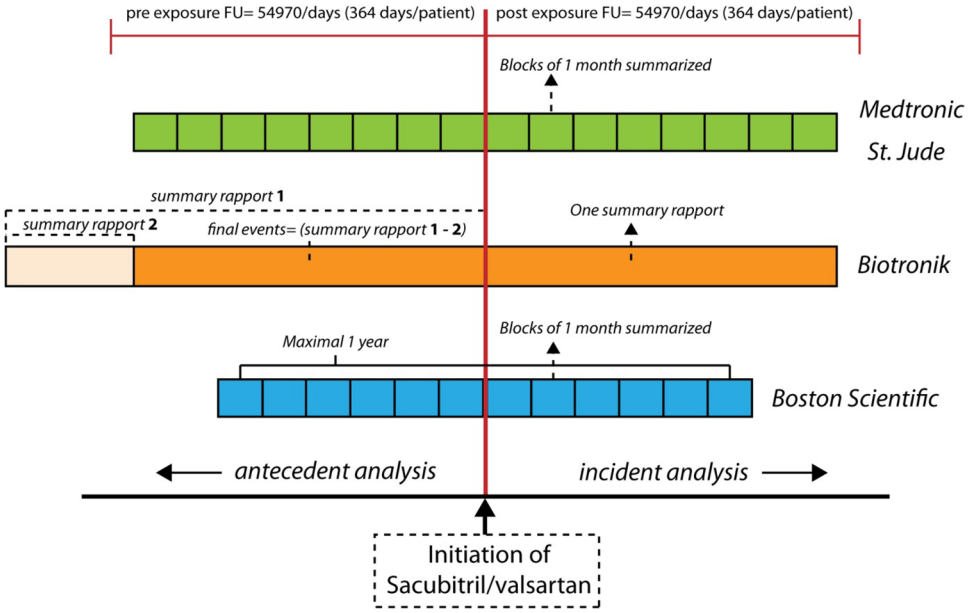

Fig. 1 Methods of generating remote tele-monitoring rapports according to vendor

devices, patients with an incident exposure time of more than 6 months were excluded as rapports are only stored going back up to 1 year for Boston scientific devices (to assure equal duration of incident and antecedent exposure time). For Biotronik devices a cumulative rapport was generated, again for matching incident and antecedent timings (see Fig. 1).

Clinical endpoints and echocardiography

For statistical analysis only parameters that are quantifiable in the tele-monitoring rapport could be analyzed. Parameters reflected as visual trends could not be included. For all vendors the amount of sustained ventricular tachycardia (VT, defined > 30 s) or ventricular fibrillation (VF), appropriate therapy, inappropriate therapy, non-sustained ventricular tachycardia (NsVT, defined as ≥ 4 beats < 30 s), mean duration of NsVT episodes, hourly premature ventricular contractions (PVCs), mean % of day in atrial tachycardia/atrial fibrillation (AT/AF), AT/AF-episodes lasting longer than 30 s, % atrial pacing and % biventricular pacing (if CRT-device) could be quantified. Patients underwent echocardiography at baseline (time of initiation of sacubitril/valsartan) and at follow-up. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson technique. The change in LVEF was calculated as the difference between the last available echocardiogram and baseline echocardiogram. An improvement of more than 5% in LVEF was defined as positive left ventricular reverse remodeling, as this was the mean in LVEF improvement following sacubitril/valsartan initiation in a previous study [11].

Statistics

Continuous variables are expressed as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Normality was checked by the Shapiro–Wilk statistic. Categorical data were expressed as numbers and percentages and compared with the Pearson χ^2 test or Fisher's exact when appropriate. Continuous variables were compared with the Student's *t* test, Mann–Whitney *U* test and paired *t* test or Wilcoxon signed-ranked test when appropriate. Statistical significance was always set at a two-tailed probability level of < 0.05. Statistics were performed using SPSS version 22 (IBM, Chicago, IL, USA).

Results

Patient population

A total of 201 patients were started on sacubitril/valsartan between December 2016 and January 2018. Of the 201 patients, 151 patients had an ICD or CRT with every patient included in a remote tele-monitoring program. Baseline characteristics of these patients constituting the final study population are reflected in Table 1. A total of 44 (29%) Biotronik, 23 Boston Scientific (15%), 43 Medtronic (29%) and 41 (27%) St. Jude devices were implanted. Patients at baseline were optimally treated with neurohormonal blockers as illustrated by Table 1. The mean % of target dose of angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker was 58 ± 30% before the initiation of sacubitril/valsartan. After switch to and uptitration of sacubitril/valsartan, the mean percent of target dose achieved was 56 ± 27%

Table 1 Baseline characteristics of overall study population

Variable	Total population ($N=151$)
Demographics	
Age, years	67.7 ± 9.9
Male	123 (82%)
Duration of heart failure, years	4.3 (1.4–8.4)
Duration of device implant, years	3.2 (0.7–7.4)
Heart failure etiology	
Ischemic	103 (69%)
Non-ischemic	47 (31%)
Physical features	
Systolic blood pressure, mmHg	122 ± 19
Diastolic blood pressure, mmHg	68 ± 11
Weight, kg	83.1 ± 15.9
BMI, kg/m^2	27.7 (25.2–30.9)
Heart rate, beats/min	67 ± 11
Comorbidities	
Atrial fibrillation	63 (41%)
COPD	22 (15%)
Hypertension	97 (64%)
Dyslipidemia	88 (58%)
Diabetes	36 (24%)
Laboratory analysis	
Sodium, mmol/l	139.4 ± 3.1
Potassium, mmol/l	4.5 ± 0.5
Serum creatinine, mg/dl	1.27 ± 0.39
NYHA class	
Class II	102 (68%)
Class III	46 (30.7%)
Class IV	3 (1.3%)
Device features	
ICD-only	46 (30.4%)
CRT-D	77 (51%)
CRT-P	28 (18.6%)
Primary prevention ICD-indication	74 (60%)
Secondary prevention ICD-indication	49 (40%)
Electrocardiogram feature	
LVEF, %	29 ± 9%
LVESV, ml	149 ± 56
LVEDV, ml	211 ± 70
Guideline-directed heart failure therapy	
ACE-I or ARB	151 (100%)
Beta-blocker	143 (95%)
Aldosterone antagonist	130 (86%)
Loop diuretic	73 (48%)
Ivabradine	17 (11%)
Digoxin	13 (9%)
Amiodarone	49 (33%)

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *ICD* implantable cardioverter defibrillator, *CRT* cardiac resynchronization therapy, *LVEF* left ventricular ejection faction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end systolic volume, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

($p=0.427$) indicating optimal uptitration. The median duration of heart failure before initiation of sacubitril/valsartan was 4.3 years (IQR = 1.4–8.4 years), indicating sufficient time for optimizing the dose of the angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker before initiation of sacubitril/valsartan. At baseline 49 patients (33%) were treated with an anti-arrhythmic therapy. This was similar throughout following. One patient underwent ventricular tachycardia ablation and was excluded from the analysis of impact on ventricular arrhythmias. Patients were followed for an average of 364 days per patient, equating to a total of 54,970 patient days being exposed to sacubitril/valsartan therapy in this cohort.

Occurrence of arrhythmias following sacubitril/valsartan

Before the initiation of sacubitril/valsartan, but under optimal treatment with neurohormonal blockers, a total of 19 individual patients developed a sustained VT/VF-episode registered according to device counters, with a total of 51 sustained VT/VF-episodes occurring before initiation of sacubitril/valsartan. Following the initiation of sacubitril/valsartan and during a similar duration of incident exposure, the amount of patients experiencing a sustained VT/VF-episode ($n=10$; $p<0.001$) and the total amount of sustained VT/VF-episodes ($n=14$; $p<0.001$) dropped significantly (see Table 2). Figure 2 illustrates the number of sustained VT/VF-episodes in patients who developed at least one episode, showing a significant reduction in the amount of sustained VT/VF-episodes in patients with at least one episode. The reduction in the amount of sustained VT/VF-episodes was also associated with a significant reduction in the amount of patients receiving appropriate therapy ($n=16$ vs. $n=6$; $p=0.007$). Indicating that the amount of longer and hemodynamically relevant episodes requiring therapy was significantly reduced. Following the initiation of sacubitril/valsartan, there was also a significant reduction in the amount and duration of NsVTs and hourly PVC-burden (see Table 2). Table 3 illustrates the change between baseline and follow-up of clinical features, laboratory features and doses of concomitant neurohormonal blockers. Indicating that changes in VT/VF burden were not directly related to changes in doses of other neurohormonal blockers, potassium or other interventions.

Following initiation of sacubitril/valsartan, the amount of sustained VT/VF was both reduced in patients with a primary prevention indication and a secondary prevention indication for their ICD. In the 74 patients with a primary prevention indication, a total of 8 patients had a sustained VT/VF before initiation vs. 4 patients following the initiation of sacubitril/valsartan ($p=0.034$). A total of 11 patients with a secondary prevention ICD suffered from a sustained VT/VF

Table 2 Evolution of remote monitoring parameters before and after sacubitril/valsartan initiation

Parameter	Before initiation ($N=151$)	After initiation ($N=151$)	p value
Ventricular arrhythmias			
Number of patients ≥ 1 VT/VF episode	19	10	< 0.001
Total amount of VT/VF-episodes	51	14	< 0.001
Number of patients with ≥ 1 appropriate therapy	16	6	0.007
Total amount of appropriate therapy-episodes	20	6	0.007
Number of patients with ≥ 1 inappropriate therapy	3	2	0.319
Total amount of inappropriate therapy-episodes	3	2	0.319
Individual patients with ≥ 1 NsVT episodes	84	67	< 0.001
NsVT (mean episodes/patient)	7.7 ± 11.8	3.7 ± 5.4	< 0.001
Mean NsVT-duration (s)	6.3 ± 5.2	5.3 ± 3.8	0.041
Mean PVCs per hour	14 (4–22)	2 (0–4)	< 0.001
Atrial arrhythmias			
Median percent of time per day in AF	9 (5–14)	9(5–14)	0.752
Patients with ≥ 1 paroxysmal AT/AF-episode > 30 s	48	33	0.159
Pacing parameters			
% of atrial pacing	7 (1–14)	7 (1–14)	0.576
% of biventricular pacing	96 ± 4	99 ± 1	< 0.001
BiV-pacing < 90%	5 (4.7%)	1 (0.9%)	0.045

VT/VF ventricular tachycardia/ventricular fibrillation, *NsVT* non-sustained ventricular tachycardia, *PVC* premature ventricular complex, *AF* atrial fibrillation, *BIV* biventricular

p values indicated the result of a paired t test if normally distributed continuous variable or Wilcoxon signed-ranked test if non-normally distributed continuous variables

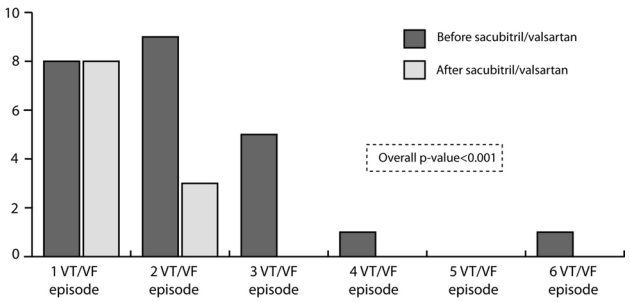

Fig. 2 Amount of VT/VF-episodes before and after initiation of sacubitril/valsartan in patients with at least one episode

episode vs. 6 patients following the initiation of sacubitril/valsartan ($p=0.017$). In patients implanted with a CRT-P, no sustained VT/VF-events occurred. Figure 3 compares the reduction in VT/VF and appropriate therapy after initiation of sacubitril/valsartan in patients with a CRT-D vs. a ICD. Indicating that both in the incident and antecedent timing, the percent of patients with a VT/VF or appropriate therapy was similar in patients with an ICD or CRT-D. Following initiation of sacubitril/valsartan, there was a numerical reduction in the VT/VF burden and percent of patients with appropriate therapy. However, this only reached statistical significance in the CRT-D group due to the larger sample size of this subgroup.

There was no significant effect in our patient population on the AT/AF-burden [mean percent of AT/AF per day before 9(5–14)% vs after 9(5–14%) $p=0.332$], the amount of patients with > 1 paroxysmal AT/AF-episodes (before $n=48$, after $n=33$; $p=0.159$) or the amount of atrial pacing [before 7(1–14)% vs after 7(1–14)%; $p=0.578$]. In parallel with the absence of an effect on atrial arrhythmias, there was also no reduction in the amount of patients experiencing inappropriate therapy following initiation of sacubitril/valsartan.

Ventricular arrhythmias in relation to reverse remodeling

A total of 110 patients (73%) had both echocardiographic measurements at baseline and follow-up. We have previously described the reverse remodeling response to sacubitril/valsartan in detail, illustrating a mean improvement in LVEF of 5% following initiation of sacubitril/valsartan [11]. In total, 48 patients (44%) had an improvement in LVEF of more than 5% following switch to sacubitril/valsartan. Approaching the hourly PVC-burden and mean NsVT-burden on a continuous scale, patients who manifested with more left ventricular reverse remodeling had a more pronounced reduction in these ventricular arrhythmias (see Fig. 4).

Table 3 Evolution of clinical, biochemical and medication features during follow-up

Parameter	At the time of initiation of sacubitril/valsartan	At final follow-up[a]	*p* value
Clinical features			
Systolic blood pressure, mm/hg	121 ± 19	116 ± 16	0.018
Weight, kg	83 ± 16	82 ± 16	0.704
Laboratory features			
Sodium, mmol/l	139 ± 3	139 ± 3	0.607
Potassium, mmol/l	4.4 ± 0.6	4.5 ± 0.5	0.280
Creatinine, mg/dl	1.34 ± 0.42	1.41 ± 0.53	0.077
Dose of neurohormonal blockers			
Beta-blocker, % of target dose	57 ± 25	56 ± 26	0.840
Spironolactone, mg	23 ± 9	23 ± 9	1.000

[a]After initiation a total of three patients underwent a percutaneous coronary intervention (one of whom had a VT/VF in the antecedent analysis), and one patient underwent a mitra-clip placement, this patient did not have VT/VF in the antecedent analysis. Not a single patient underwent AV-nodal ablation in the antecedent analysis

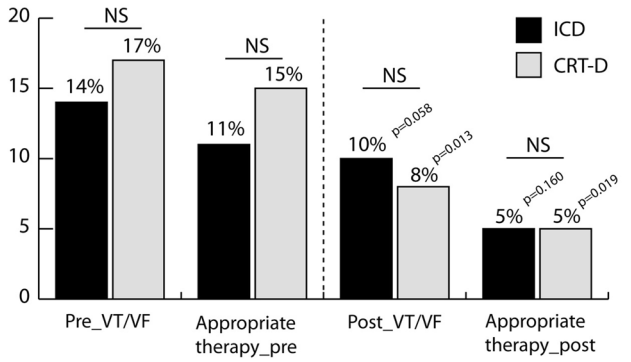

Fig. 3 Ventricular arrhythmias in CRT-D vs. ICD patients in relation to sacubitril/valsartan initiation. *NS* non-significant. *p* values in italics are the result of paired *t* testing

Change in PVC-burden in relation to BiV-pacing

Following the initiation of sacubitril/valsartan, there was a statistical improvement in the degree of BiV-pacing in patients with a CRT-device. Of note, the degree of BiV-pacing was generally already high at baseline (% BiV-pacing 96 ± 4%; see Table 2). Before initiation of sacubitril/valsartan a total of 5 patients had < 90% BiV-pacing. Following initiation of sacubitril/valsartan only 1 patient had a < 90% BiV-pacing (*p* value for difference = 0.045). Following initiation of sacubitril/valsartan there was a reduction in the median PVCs per hour for the entire patient population (see Table 2). The four patients who exhibited an improvement in BiV-pacing to more than 90% following initiation of

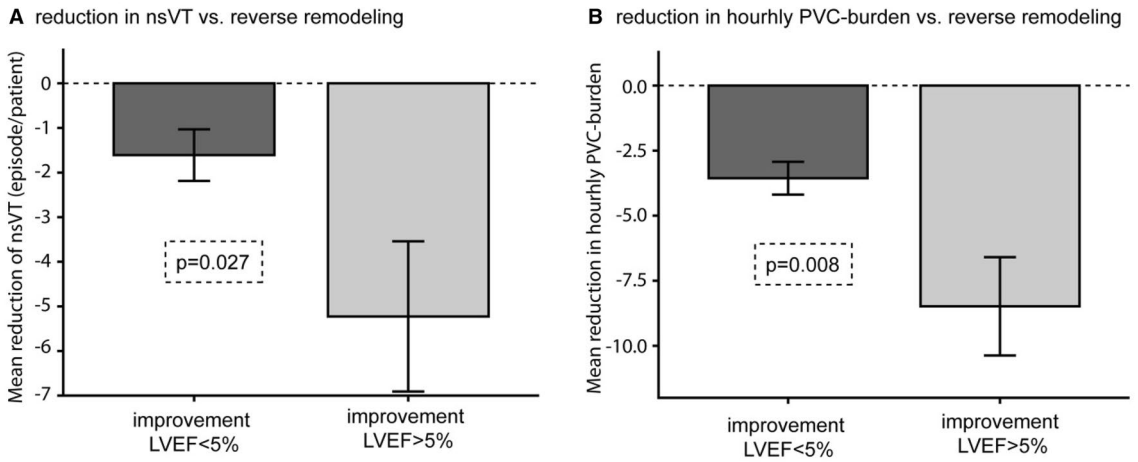

Fig. 4 Ventricular arrhythmias in relation to reverse remodeling. Bars indicate mean ± standard error mean

sacubitril/valsartan, exhibited a more pronounced reduction in hourly PVC-burden in comparison to the patient with a persistent percent of BiV-pacing below 90% (−77 PVCs per hour reduction vs −8 PVCs per hour reduction; $p=0.006$). An example of a patient showing significant reductions in PVC-burden is reflected in Fig. 5.

Discussion

In contrast to PARADIGM-HF population, our patient population with very high class I recommended penetration of device therapy, offers the unique opportunity to investigate arrhythmia burden pre- and post-initiation of sacubitril/valsartan. The risk of ventricular arrhythmias and appropriate therapy is significantly reduced after initiation of sacubitril/valsartan [12]. Furthermore, our analysis generates the hypothesis that this effect is mediated to some extent by beneficial left ventricular reverse remodeling.

A recent regression meta-analysis indicates that over the last 2 decades, the annual risk for SCD in heart failure patients with reduced ejection fraction has decreased from 6.5 to 3.3% through the employment of guideline-directed heart failure pharmacotherapy [1]. Sacubitril/valsartan forms the latest supplement to these background pharmacologic therapies, generating benefit on cardiovascular endpoints through the modulation of the natriuretic peptide pathway [2]. In the PARADIGM-HF trial, sacubitril/valsartan resulted in a lower risk for dying from SCD (HR = 0.80; CI = 0.68–0.94; $p=0.008$). Importantly, in randomized controlled clinical trials investigating medicines, this endpoint is often retrospectively adjudicated based on limited clinical information and based on arbitrary definitions. Therefore, it remains difficult to determine the exact etiology of the SCD-event. For instance, of all 604 deaths defined as SCD in the PARADIGM-HF trial, only 44 were resuscitated sudden deaths, where an arrhythmic event is often more tangible [2]. Our data, based on device analysis, suggest that the reduction in SCD is indeed (partially) mediated through a reduction in ventricular tachyarrhythmias. This is also important as the PARADIGM-HF trial is often criticized for the very low rate of ICD-utilization (7% CRT, 14.9% ICD). As sacubitril/valsartan seems to reduce ventricular arrhythmias, it suggests that optimal utilization of ICDs in the PARADIGM-HF trial could have prevented additional cases of SCD.

In addition to modulating the angiotensin–renin–aldosterone system, sacubitril/valsartan enhances the effect of natriuretic peptides, which results in multiple beneficial effects through improved natriuresis and diuresis, decreasing sympathetic tone, decreasing cardiac fibrosis and inducing beneficial hemodynamic alterations of cardiac reverse remodeling [13]. The occurrence of ventricular arrhythmias in heart failure is based on numerous factors initiating the rhythm disturbances (PVCs, enhanced automaticity, etc.) and perpetuating/maintaining the event (cardiac fibrosis, dyssynchrony, conduction velocity delays, repolarization dispersion, etc.) [14]. Sacubitril/valsartan reduces NT-proBNP and mitigates the echocardiographic presence of a restrictive mitral filling pattern [11, 15]. A high NT-proBNP, which reflects the presence of increased wall stress, is an independent predictor of ventricular arrhythmias in heart failure [16]. Indeed, enhanced wall stress is associated with enhanced activity of stretch-sensitive sodium, potassium and calcium membrane channels, resulting in more triggers (e.g., PVCs) and "maintenance substrate" (conduction velocity delays and repolarization dispersion) for ventricular arrhythmias [14]. Experimental animal heart failure models indicate that

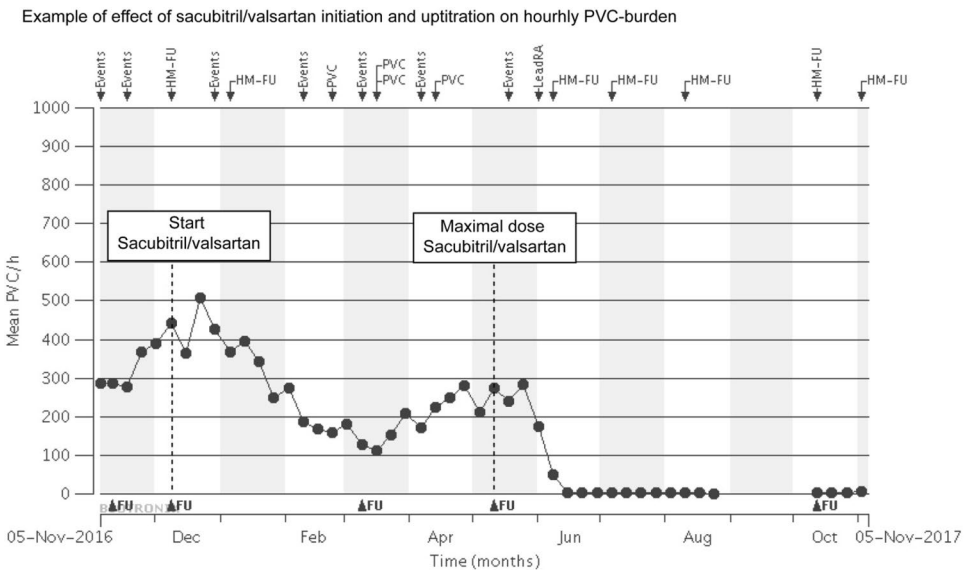

Fig. 5 Change in PVC-burden following sacubitril/valsartan

enhancing left ventricular diastolic pressures induces PVCs, and this to a higher degree if underlying systolic function is depressed [17]. De Diege et al. illustrated that a reduction in NT-proBNP was positively correlated with a reduction in hourly PVC-burden following initiation of sacubitril/valsartan [18]. Our data perhaps also indicate that in addition to this, an improvement in underlying systolic function reduces PVC, NsVTs and sustained ventricular arrhythmias of VT/VF. This resulted in a lower prevalence of appropriate therapy. However, numerous other mechanisms related to initiation of sacubitril/valsartan could be responsible for the observed reduction in ventricular arrhythmias (e.g., reduction in fibrosis, modulation of the sympathetic nervous system). Furthermore, there was also a slight increase in percent of biventricular pacing, which could also explain the improvement in LVEF, and hereby influence the risk of ventricular arrhythmias [19–21].

In our population with a mean follow-up of 364 days, the 1 year prevalence of appropriate therapy was 3.9% after initiation of sacubitril/valsartan, which is in the similar range of SCD as in the PARADIGM-HF (3.3% per year) [1]. Although perhaps some cases of SCD could have been prevented in the PARADIGM-HF trial with a more robust background treatment of ICDs, our data also indicate that with implementation of optimal pharmacotherapy the risk for developing a substrate for anti-tachycardia interventions by an ICD diminishes. Again underscoring the importance of appropriate primary prevention ICD allocation in patients with heart failure with reduced ejection fraction [6].

In line with the PARADIGM-HF trial, we did not find a beneficial effect of sacubitril/valsartan therapy on atrial arrhythmias [22]. Both the total burden of AT/AF and the amount of paroxysmal episodes was similar after initiation of sacubitril/valsartan in comparison to before. In line with this observation we did also not notice a reduction in the occurrence of inappropriate therapy, which is often due to rapidly conducting atrial arrhythmias.

Similar to De Diege et al., we noticed a slight improvement in the percent of biventricular pacing following initiation of sacubitril/valsartan [18]. This improvement, was correlated with the reduction in hourly PVC-burden. In addition to rapidly conducted atrial arrhythmias (which were not reduced in our analysis), a high PVC-burden is a well known reason for suboptimal CRT-delivery [23].

Limitations

This was not a placebo-controlled trial but instead a retrospective analysis of real-world patients using an antecedent vs. incident analysis. Such analysis might be liable to the effect of initiation of other treatments. However, patients were optimally treated before initiation of sacubitril/valsartan as illustrated by the higher coverage of class-I lifesaving heart failure therapies. Furthermore, patients did not receive more anti-arrhythmic therapies during follow-up. Hereby making the observed reduction in ventricular arrhythmias likely related to the initiation of sacubitril/valsartan. We did not have measurements of NTproBNP (decrease) or BNP (increase) to document treatment effect, as these biomarkers are not reimbursed in Belgium. Our analysis is limited to patients with an implantable cardiac device capable of offering remote tele-monitoring, which clearly forms a higher risk patient population in comparison to patients without a device. Finally, given the lower number of sustained VT/VF-episodes in comparison to hourly PVC-burden or NsVT it was not possible do compare sustained VT/VF-episodes in patients with more left ventricular reverse remodeling following sacubitril/valsartan initiation. Nevertheless, numerous studies have indicated that NsVTs are well correlated with the development of more sustained and hemodynamically relevant ventricular arrhythmias, and reduction of NsVT has been used a surrogate marker indicating reduction in the VT/VF-risk [24, 25].

Conclusions

In patients with heart failure with reduced ejection fraction and a guideline-recommended class I indication for sacubitril/valsartan, initiation of sacubitril/valsartan is associated with a lower degree of ventricular arrhythmias, resulting in less ICD-interventions. This beneficial effect on ventricular arrhythmias might be mediated by cardiac reverse remodeling. Pieter Martens has received consultancy fees from Novartis. Wilfried Mullens has received an unrestricted research grant from Novartis.

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