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Angioedema in heart failure patients treated with sacubitril/valsartan (LCZ696) or enalapril in the PARADIGM-HF study

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ABSTRACT

Background: PARADIGM-HF demonstrated significant clinical benefits for sacubitril/valsartan (LCZ696, an angiotensin receptor neprilysin inhibitor) versus the angiotensin-converting enzyme inhibitor (ACEI) enalapril in patients with heart failure with reduced ejection fraction. As inhibition of ACE, and co-inhibition of ACE and neprilysin, may increase the risk of angioedema, this was an adverse event of special interest.
Methods: Following sequential enalapril and sacubitril/valsartan run-ins, patients were randomized to twice-daily sacubitril/valsartan 200 mg or enalapril 10 mg. The study design incorporated two wash-out periods (~36 h each) to minimize any potential risk of angioedema due to overlapping ACE and neprilysin inhibition. Suspected cases of angioedema were reported to, and blindly adjudicated by, an independent angioedema adjudication committee (AAC).
Results: Of the 10,513 patients entering the enalapril run-in, 9419 entered the sacubitril/valsartan run-in and 8432 received double-blind treatment. Overall, 148 suspected angioedema events occurring in 144 patients were reported to AAC, with one event reported during screening period. Of the remaining 147 events, 54 were confirmed as angioedema by AAC. A confirmed event was experienced by 15 (0.14%) and 10 (0.11%) patients, during the enalapril and sacubitril/valsartan run-ins, respectively, and by 10 (0.24%) and 19 (0.45%) patients in the corresponding randomized arms during the double-blind phase. The frequency of confirmed angioedema was higher in black patients. Most events were mild. Only five patients required hospitalization and none required mechanical airway support.
Conclusion: The number of confirmed angioedema events in PARADIGM-HF was low and there was no-marked excess risk of angioedema with sacubitril/valsartan versus enalapril.

1. Introduction

Sacubitril/valsartan (LCZ696) is an angiotensin receptor neprilysin inhibitor (ARNI) that acts on the renin-angiotensin-aldosterone system (RAAS) through angiotensin II (AT II) antagonism and simultaneously augments the natriuretic peptide (NP) system, which plays a compensatory role when the RAAS is chronically activated [1,2]. In the landmark PARADIGM-HF trial, sacubitril/valsartan was superior to the angiotensin-converting enzyme inhibitor (ACEI), enalapril, in preventing deaths and HF hospitalization in chronic HF patients with reduced ejection fraction (HFrEF) [3,4]. Based on the results from the PARADIGM-HF trial, sacubitril/valsartan was recently approved for the treatment of patients with HFrEF in the USA, Europe, and many other countries worldwide.

Safety analyses from the PARADIGM-HF trial demonstrated that sacubitril/valsartan was generally well tolerated as compared with enalapril. Rates of study discontinuations due to adverse events (AEs) were lower in patients randomized to sacubitril/valsartan compared with the enalapril group (10.7% versus 12.3%, nominal p = 0.03) [3].

The risk of angioedema is known to be increased with the use of ACEIs [5,6], and this risk may be augmented by the inhibition of neprilysin; this AE was, therefore, of special interest in the PARADIGM-HF trial. This paper provides a comprehensive overview of the identification, reporting, adjudication, and outcomes of angioedema events reported during the PARADIGM-HF trial.

2. Methods

In this report, analysis of the occurrence of angioedema as an AE in heart failure patients treated with sacubitril/valsartan or enalapril in the PARADIGM-HF trial is presented.

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2.1. PARADIGM – HF study design

As previously reported [2,3], PARADIGM-HF was an event-driven, multinational, randomized, double-blind study comparing sacubitril/valsartan with enalapril in adult patients (N = 8442) with chronic NYHA class II–IV heart failure with reduced ejection fraction (initially left ventricular ejection fraction ≤40%, changed to 35% via a protocol amendment), in addition to other heart failure therapy [3]. The comprehensive inclusion/exclusion criteria have been reported previously [3]. Importantly, patients with a history of angioedema or with a history of intolerance to ACEI or ARB therapy were excluded from the study.

The primary endpoint of the PARADIGM-HF study was a composite of death from cardiovascular causes or a first hospitalization for heart failure and consisted of three phases: screening; single-blind enalapril run-in followed by single-blind sacubitril/valsartan run-in; and randomized, double-blind treatment (Supplementary Appendix **Fig. S1**) [3]. During the single-blind, active run-in period, patients received enalapril 10 mg twice daily (bid) for 2 weeks, followed by sacubitril/valsartan 100 mg bid up-titrated to 200 mg bid over 4–6 weeks. Patients were required to discontinue any ACEI/ARB pre-study medication prior to the run-in period. The study design consisted of two wash-out periods of approximately 36 h each to minimize any potential risk of angioedema due to overlapping of ACE inhibition and neprilysin inhibition. The first wash-out occurred after completing the enalapril run-in period and prior to beginning of the sacubitril/valsartan run-in period; and the second after completing the sacubitril/valsartan run-in. Patients were then randomized to receive sacubitril/valsartan 200 mg bid or enalapril 10 mg bid during the double-blind period [2,7].

2.2. Safety assessment

Patients were assessed at each study visit and safety assessments consisted of collecting all AEs, their severity, and their relationship to the study drug. AEs, in general, were detected through non-directive questioning of the patient at each visit, or volunteered by the patient, or through physical examination, or related assessment(s) (i.e., laboratory tests).

Investigators and clinical monitoring personnel were provided with a list of MedDRA preferred terms to consider when monitoring for angioedema (Supplementary Appendix **Table S1**). Investigators were instructed to pay special attention to any swelling, edema, or other symptoms that resembled angioedema or angioedema-like events reported by patients, regardless of whether they thought it was angioedema. A Case Report Form and Adjudication Questionnaire for an Angioedema-like Event were completed with appropriate accompanying documentation (i.e., physical examination findings, diagnostic tests, and hospital discharge summary, and death certificate if appropriate). Reported angioedema or angioedema-like events were adjudicated by an angioedema adjudication committee (AAC). The AAC was an independent group of experts in the diagnosis and treatment of clinical angioedema who were blinded to treatment allocation during the study (the AAC members are listed in the Supplementary Appendix). Each member reviewed the suspected reported events of angioedema in a uniform and consistent manner and assessed the severity of adjudicated events (Table 1). In the absence of a unanimous decision in diagnosis or severity grading, additional information was sought. If unanimity was still not achieved, a majority opinion was accepted. The final assessment by the AAC was entered on the Angioedema Adjudication Assessment Form, which was added to the study database.

Table 1
Severity of AAC-confirmed angioedema events in the run-in and double-blind period (severity grade per adjudication).[a]

	Run-in		Double-blind	
	Enalapril N = 10,513	Sacubitril/valsartan N = 9419	Enalapril N = 10,513	Sacubitril/valsartan N = 9419
Grade I, n (%) (No treatment administered or antihistamines only)	8 (0.08)	8 (0.08)	5 (0.12)	10 (0.24)
Grade II, n (%) (Treated with catecholamines or steroids)	6 (0.06)	2 (0.02)	4 (0.09)	6 (0.14)
Grade III, n (%) (Hospitalized but no mechanical airway support)	1 (0.01)	0 (0.00)	1 (0.02)	3 (0.07)
Grade IV, n (%) (Mechanical airway protection or death from airway compromise)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

N, patients who received study drug; n, patients with events.
AAC, Angioedema Adjudication Committee; SAE, serious adverse event.
[a] Of these events, 3 (0.03%) and 1 (0.01%) were reported as SAEs during the run-in phase, and 4 (0.09%) and 4 (0.10%) were reported as SAEs during the double-blind phase for enalapril and LCZ696, respectively.

Additionally, the clinical database was monitored on a regular basis by the sponsor using the same list of MedDRA preferred terms provided to the investigators. Suspected angioedema or angioedema-like events identified by sponsor were reported to the AAC by the investigators and adjudicated by the AAC as described above.

2.3. Analysis

Safety assessments were evaluated separately for both the run-in period and the double-blind period and additionally, for the entire study duration by combining run-in and double-blinded periods together (events occurring during both the sacubitril/valsartan run-in and double-blind period; and during both the enalapril run-in and double-blind period). The overall incidence rates are presented in frequency tables. Subgroup analyses were reported for race (black and non-black) and current smoker status. The time-to-first confirmed angioedema event and the cumulative rates were estimated by Kaplan-Meier method and presented graphically.

3. Results

A total of 10,521 patients were enrolled in the PARADIGM-HF study, of which 10,513 and 9419 patients were exposed to enalapril and sacubitril/valsartan during the run-in period, respectively. A total of 8442 patients were randomized in a 1:1 ratio to the sacubitril/valsartan and enalapril treatment arms and 8432 patients (safety set) were exposed to the study medication during the double blind phase (4203 and 4229 patients receiving sacubitril/valsartan and enalapril, respectively) (Fig. 1).

3.1. Combined run-in and double-blind treatment period

Overall, there were 148 suspected angioedema events in 144 patients reported to the AAC. One event was reported from the screening period before the start of the study. Of the remaining 147 events, 54 were adjudicated as confirmed angioedema. Out of the 54 confirmed angioedema events, 25 events (25/10,513 patients [0.24%]) occurred during the run-in period and 29 events (29/8432 patients, 0.34%) events during the double-blind period (Fig. 1, Table 2). Of these events, 48 were assessed as suspected to be related to the study medication (Table 2).

Most events of confirmed angioedema were of severity grades I and II (treated with antihistamines, catecholamines, or steroids or did not require treatment). Five cases required hospitalization, but no events of reported angioedema resulted in airway compromise or a need for mechanical ventilation. There were no angioedema-related fatalities (Table 1).

Kaplan Meier estimates of the combined run-in and double-blind periods revealed the cumulative rate estimates at Day 180 of 0.40 (95% CI 0.25, 0.61) for sacubitril/valsartan and 0.24 (95% CI 0.14, 0.38) for enalapril (Supplementary Appendix **Table S2**).

3.2. Run-in period

A total of 15/10,513 patients (0.14%) had confirmed events of angioedema during the enalapril run-in and 10/9419 patients (0.11%) had confirmed events during the subsequent sacubitril/valsartan run-in. There were 8 events of grade I and 6 events of grade II severity during the enalapril run-in and 8 events of grade I and 2 events of grades II severity during the sacubitril/valsartan run-in (Table 1). One case of severity grade IIIa angioedema occurred in the enalapril run-in group and required hospitalization (Table 1). Angioedema led to study drug discontinuation in all 15 cases in the enalapril run-in period, and in 8 of 10 cases in the sacubitril/valsartan run-in period. Of the patients who continued in the study, one was randomized to enalapril and the other to sacubitril/valsartan, and no recurrence of angioedema was reported in these two patients.

3.3. Double-blind treatment period

During the double-blind treatment period, 19/4203 patients (0.45%) in the sacubitril/valsartan group and 10/4229 patients (0.24%) in the