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Non-Interventional Study Final Report

Assessment of Real LIfe cAre – Describing EuropeaN Heart FailurE Management (ARIADNE)

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1 Abstract

Title

Assessment of real life care – describing European heart failure management (ARIADNE)

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Keywords

Heart failure management, sacubitril/valsartan, standard of care, Europe

Rationale and background

Although Heart Failure (HF) was responsible for approximately 1.6 million hospitalizations per year in the EU recently as judging by ICD-10 I50 coding reported by Eurostat (Eurostat 2014), comprehensive epidemiological data spanning the continent have begun to emerge only relatively recently. In Germany alone, HF was responsible for 386,548 hospitalizations and 46,410 deaths in 2012 as judging by ICD-10 I50 coding reported by the Federal Statistical Office (Statistisches Bundesamt 2013).

With HF mortality remaining at unacceptably high rates, novel treatment approaches are urgently needed. Sacubitril/valsartan (S/V, also called LCZ696) constitutes the first of a new class of drugs – Angiotensin Receptor-Neprilysin Inhibitors, ARNIs – designed to replace the current role of ACE inhibitors or Angiotensin receptor blockers (ARBs) in the management of HF. In a phase III trial (PARADIGM-HF), S/V at a target dose of 200 mg BID reduced cardiovascular mortality by 20% compared to an evidence-based dose of the ACE inhibitor enalapril (10 mg BID) (McMurray, Packer et al. 2014). While PARADIGM-HF established a superior efficacy of S/V with a safety profile comparable to that of enalapril, it appears extremely important to gather additional data on its use and effectiveness in a real life setting, such as which patients are started on S/V; the pattern of administration of the drug at start and the proportion of patients able to tolerate the drug at different doses; the impact on healthcare resource utilization; quality of life (QoL) as well as main efficacy and safety events in a real-life setting with a more diverse set of patients.

The above mentioned questions are addressed within the present prospective non-interventional study (NIS). ARIADNE planned to enroll and describe 9.000 symptomatic CHF patients with reduced left ventricular ejection fraction (HFrEF) treated by specialists in an office-based setting across European countries: 4500 patients treated with current standard of care (SoC) and 4500 patients on S/V. Enrollment in both cohorts started in each single country when S/V was available for use in clinical practice.

Research question and objectives

The main objectives of the present NIS were to provide an European picture of (i) the demographic and clinical features of HFrEF patients managed in the outpatient sector and the diagnostic and pharmacological interventions they receive and (ii) the demographic and clinical features of patients for whom the treating physician decided to start sacubitril/valsartan, the pattern of administration of this drug, the diagnostic and therapeutic interventions these patients receive and the safety and tolerability profile of this drug in real life.

Study design

This was a multicenter, multi-country and prospective NIS conducted in 17 European countries. Symptomatic CHF patients with HFrEF managed in the outpatient sector were eligible for enrollment. Patients could be treated with both, individualized SoC and S/V. For a period of one year, the administration of treatment, diagnostic and therapeutic interventions and therapeutic effects in terms of symptom control and QoL improvement were to be recorded.

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Setting

Each patient was to be observed for a period of one year. After the baseline visit (Visit 1) two follow-up visits in semi-annual intervals were foreseen.

Subjects and study size, including dropouts

In total, 687 study centers in 17 European countries (Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Ireland, Israel, Italy, Malta, Norway, Russia, Slovakia, Spain, Switzerland, UK) collected data of 9069 patients (between 1 – 90 patients per study center). 282 patients (3.1%) were excluded from the analysis due to violation of minimum criteria for analysis (e.g. violation of inclusion/exclusion criteria, no valid investigator signature, protocol deviations, etc.).

2449 analyzed patients (27.9%) did not complete the study. The most frequent reason for discontinuation was a missed annual visit (n=682, 27.8% of patients with discontinuation, 7.8% of all analyzed patients).

Variables and data sources

This was an observational study with prospective data collection. For some variables, retrospective data was obtained from the patients' medical records (e.g. healthcare utilization in the past 12 months, medical history). The study comprised three visits: at baseline and at approximately 6 months and 12 months after baseline. The investigator or his/her designee entered the data directly into the electronic Case Report Form (eCRF) using the Clincase® system (Quadratek Data Solutions, version 2.6.0.34).

Statistical methods

All results were based on descriptive analyses, i.e. analyses were based on percentages for categorical data or summary statistics for quantitative data. Additionally, 95% confidence intervals were added.

Results

Patient characteristics

The mean age of all patients was 68.1 years (S/V: 67.3 years, SoC: 68.9 years), with 30.3% being older than 75 years. and the gender distribution showed an obvious male preponderance (76.1% overall, S/V: 76.4%, SoC: 75.8% males).

Most patients had been diagnosed with HF several years before study inclusion, with a mean time since diagnosis of about 5.6 years overall (S/V: 5.7 years, SoC: 5.4 years). The etiology of HF was most often cardiac ischemia (58.4%), followed by hypertension (34.9%) and cardiac arrhythmia (16.4%). The majority of patients were in NYHA class II (61.3%), or NYHA class III (37.1%), with a mean LVEF of 34.0%. However, still more than a third of the patients (38.6%) suffered from moderate to severe limitations (NYHA class III/IV). Notably, the LVEF was slightly lower in the S/V group than in the SoC group (S/V: 32.7%, SoC: 35.4%).

As expected in this patient cohort diagnosed with HF, and in light of the documented etiologies of HF, most frequent comorbidities included arterial hypertension, coronary heart disease and dyslipidemia. More than every tenth patient (11.2%) had a history of myocardial infarction upon inclusion in the study.

Treatment response

Throughout the study, the proportion of patients in NYHA class III or IV decreased in the course of the study from 38.6% to 24.6% (the decrease corresponding to an increase of patients with NYHA I). Notably, patients in the S/V group started out with a higher rate of severe NYHA classes III and IV. Overall, patients became less symptomatic based on NYHA classification in both treatment groups in the course of the study. Consistently, mean LVEF increased during the study in both patient groups. However, high rates of missing echocardiography preclude comprehensive interpretation.

The most frequently reported pre-defined HF symptoms at V1 were dyspnea on effort (95.9%), followed by fatigue (68.2%). At baseline, symptoms tended to be more severe in patients in the S/V group

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compared to SoC. Over the course of the study, almost all symptoms became less common in both treatment groups.

Overall, in light of similar numbers of non-completers in both groups (i.e. similar rates of patients not attending visits 2 and 3), more patients in the S/V seemed to shift to less severe symptom categories than in the SoC group. However, this remains speculative, as non-completers may have been more severely ill, thus not allowing for unbiased comparison between the groups.

Serum potassium and serum creatinine was similar in both groups and remained stable in the course of the study. Notably, the median BNP at V1 was higher in the S/V group (395.5 pg/ml) than in the SoC group (287 pg/ml). In the course of the study, the median value decreased in both groups to 258 pg/ml in the S/V group and 221 pg/ml in the SoC group at V3. Similarly, the median NT-proBNP at V1 was higher in the S/V group (1133.5 pg/ml) than in the SoC group (998 pg/ml). The median value decreased also in both patient groups during the study to 882 pg/ml in the S/V group and 569 pg/ml in the SoC group at V3.

The renal function, as measured by mean eGFR, was better in the S/V group compared to the SoC group at V1 (78.0 ml/min vs.74.8 ml/min). In both patient groups, renal function (mean eGFR) worsened slightly in the course of the study to 75.4 ml/min (S/V group) and 72.0 ml/min (SoC group), respectively, at V3.

Patient-reported outcomes

The mean EQ-5D utility index decreased (signifying worsening state of health) in the course of the study (change from V1 to V3-LOCF: -0.020 in the S/V group and -0.051 in the SoC group).

Notably, the mean KCCQ overall summary score, a score more specifically designed to address patients with cardiomyopathy, increased (signifying an improved health state) in the course of the study in the S/V group (change from V1 to V3-LOCF: 1.9), yet decreased in the SoC group (change from V1 to V3-LOCF: -1.9).

HF treatment

Standard of care

More than two thirds (68.8%) of S/V patients and 18.0% of SoC patients were ACEi/ARB naïve, i.e. did not receive ACEi and/or ARB prior to study start. 81.6% of patients were on prior beta-blockers, 55.0% received MRA, and 61.3% loop diuretics. Throughout the study concomitant HF medication remained largely stable with no considerable changes regarding drug classes and corresponding combinations.

S/V

Average documented treatment duration of S/V within ARIADNE was more than one year (368.2 days). The majority of patients initiated treatment with a dosage of 50 mg BID (53.4%), followed by 100 mg BID (32.1%). Only 37.3% patients achieved the target dose as per SmPC of 200 mg BID, while almost as many patients (34.5%) achieved only 100 mg BID.

In patients reaching the target dose of 200 mg BID any time during the study (38.2%), most achieved this dose within 1 titration steps (61.0%). Patient required on average slightly more than three months (104.4 days) until the target dose was reached. The majority (84.0%) was also able to maintain this target dose for at least 12 weeks.

The most common cause of a discontinuation (25.7%), or for a downtitration/omitted uptitration (49.4%) was hypotension. Notably, in 300 patients (6.0%), off-label use was detected, the most frequent cause being concomitant intake of ACEi or ARB (79.7%, 239 patients).

Main objectives

Patient profiles at S/V initiation - objective (i)

For the comparison of patient profiles at S/V inititation, the S/V group was restricted to patients that started S/V ±1 month around baseline.

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The main patient characteristics did not differ considerably between patients with S/V initiation vs. those continued on SoC: particularly, mean age was similar in both groups (68.0 years in the S/V group, 68.9 years in the SoC group), as well as the gender distribution with its obvious male preponderance (S/V: 75.0%, SoC: 75.8% males).

Most patients had been diagnosed with HF several years before study inclusion, with a mean time since diagnosis of 5.4 years in both groups. The etiology of HF was most often cardiac ischemia (S/V: 60.1; SoC: 58.1%), followed by hypertension (S/V: 37.1; SoC: 35.3%), other (S/V: 23.1; SoC: 21.1%) and cardiac arrhythmia (S/V: 13.5; SoC: 11.0%).

The percentage of patients with NYHA class III/IV was higher in the S/V group compared to the SoC group (S/V: 50.3%, SoC: 32.1%). Notably, the LVEF was slightly lower in the S/V group than in the SoC group (S/V: 32.3%, SoC: 35.4%).

In addition, some prespecified heart failure symptoms, e.g. moderate to severe dyspnea on effort, were more frequent in the S/V group at baseline (S/V: 60.6%, SoC: 49.4%). Similarly, S/V patients were more often hospitalized in the 12 months prior to baseline visit (S/V: 44.0%, SoC: 39.3%), they had higher BNP/NT-proBNP levels (BNP - S/V: 1021.4 pg/ml, SoC: 742.9 pg/ml; NT-proBNP - S/V: 2456.8 pg/ml, SoC: 2441.6 pg/ml), and a higher CV device use at baseline (S/V: 47.9%, SoC: 41.2%). No marked group differences were observed with respect to comorbidities. The rate of patients experiencing transient ischemic attacks prior to baseline was slightly higher in the S/V group (7.2%) compared to the SoC group (5.7%).

Patient profiles depending on achievement of target dose - objective (ii)

Patients who maintained and achieved the target dose of 200 mg BID were younger (65.4 vs. 68.3 years; fewer patients in the age bracket > 75 years), and had less often the clinically more severe NYHA stages III and IV, than the patients who did not achieve the target those, or those who achieved it but did not maintain it for 12 weeks. Comorbidities also varied depending on achievement of the target dose: atrial fibrillation and coronary heart disease, renal diseases, as well as malignant diseases were more common in the group that did not achieve the target dose; on the other hand, type 2 diabetes mellitus and obesity were more common in patients achieving and maintaining the target dose.

Adverse events

In total, 5433 AEs were reported in 2241 patients taking S/V anytime during study (45.2%). 1891 events were reported as SAEs and occurred in 1063 patients (21.4%). A total of 871 ADRs were reported in 651 patients (13.1%). The most frequently reported ADRs (by PT) were hypotension (6.5% of patients), followed by hyperkalaemia (1.0%). Overall, 371 AEs led to permanent discontinuation of S/V treatment in 180 patients (3.6%). Twenty-eight patients (0.6%) discontinued S/V treatment due to SAEs.

The most frequently reported AEs were related to system organ classes (SOC's) cardiac disorders (16.0% of patients) and vascular disorders (10.4%), which are expected adverse events in this patient population. The most frequently reported PTs were hypotension (7.9% of patients) and cardiac failure (6.9%). All other PTs occurred each in less than 3% of patients. Generally, observed rates of AEs are below those of controlled clinical trials which reflects the nature of non-interventional studies.Generally, AE reports were in line with the approved summary of product characteristics for S/V. Among the SAEs, the most frequently reported PTs were cardiac failure (5.2% of patients), atrial fibrillation (1.3%) and pneumonia (1.0%). All other PTs occurred each in less than 1% of patients.

For 46 patients, a PT related to death was reported. That is, PT death was reported in 38 patients, sudden cardiac death in 6 patients and sudden death in 2 patients.

Discussion

A large cohort of HF patients (9069) from multiple European countries was enrolled in the ARIADNE study. The collection of follow-up data on e.g., morbidity, ongoing medication, estimates of quality of life, and resource utilisation, the registry provides a comprehensive picture of real-world HF patients in various European countries. Patient characteristics, particularly the advanced age and the male predominance, are largely in line with the known epidemiology of patients with HF and reduced ejection

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fraction (Lloyd-Jones, Larson et al. 2002, Pandey, Omar et al. 2018). Also the documented underlying etiologies for HF are consistent with the literature (Kannel, Ho et al. 1994, Gheorghiade and Bonow 1998,He, Ogden et al. 2001), as well as data on the rate of concomitant HF medications (Maggioni, Anker et al. 2013).

This study was initiated shortly after market approval of S/V, thus largely reflected the previous SoC use, and offered first insights into the initial phase of introducing S/V into real-world treatment routine.

Treatment groups were largely similar, with a slightly lower age, contrasted by a somewhat higher disease burden in the S/V group compared to the SoC group, e.g. reflected by lower LVEFs and more patients with more severe NYHA classes III/IV. This group differences are also in line with previous data from the CHAMP-HF study (DeVore, Hill et al. 2018).

Notably, 18.0% of SoC patients and even 68.8% of S/V patients being ACEi/ARB-naïve raises the question on the quality of the local medical care: the patients in ARIADNE were symptomatic upon inclusion, and should therefore have been on effective HF treatment. Also throughout the study, while most patients remained symptomatic, only a few patients underwent treatment adjustments with regards to drug classes. As per the ESC guidelines, patients with symptomatic HF and reduced ejection fraction should receive maximally tolerated therapy with ACEi/ARB along with a beta-blocker as a first-line treatment. If still symptomatic, an MRA should be added. If symptoms still persist, S/V is recommended to replace ACEi in ambulatory HFrEF patients who remain symptomatic despite optimal therapy (Ponikowski, Voors et al. 2016). However, a recent expert consensus of the ESC stated that treatment with S/V may also be safe in ACEi/ARB-naïve patients, thereby providing (retrospective) justification of the treatment pattern used in many ARIADNE patients (Seferovic, Ponikowski et al. 2019).

Guideline adherence was generally low at baseline, even though at this point a presumptive treatment optimization had already taken place. Adherence was markedly higher adherence in the S/V group (overall 44%, S/V: 51.4%, SoC: 37.3%). When taking into account guideline-recommended dosages, adherence at baseline was even much lower (overall: 18.0%, S/V: 23.8%, SoC: 12.2%). By end of the study, there was a slight increase of adherence (overall: 20.1%, S/V: 26.5%, SoC: 13.4%). It appears plausible that patients treated with the novel S/V drug, followed ESC guidelines generally more stringently (Seferovic, Ponikowski et al. 2019).

The most frequently documented S/V treatment regimens are mostly compliant with the SmPC of Entresto®. However, a substantial number of patients (6.0%) used S/V in an off-label context, e.g., due to concomitant intake of an ACEi or an ARB. Notably, a relatively large proportion of patients initiated S/V at 50 mg BID, and the maximal dosage remained in many cases at 100 mg BID. According to the SmPC, recommendations for a reduced starting dose are very specific and concern patients with a moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2) or patients with at least moderate hepatic impairment (Child Pugh B or AST/ALT value more than twice the upper limit of the normal range), or patients with a systolic blood pressure between ≥ 100 to 110 mmHg. In addition, patients not on current ACEi or ARB therapy upon S/V initiation should specifically start with the reduced starting dose of 50 mg BID, as stated in the SmPC. As more than two thirds of patients receiving S/V (68.8%) were ACEi/ARB naïve, the reduced starting dose appears to have been indeed justified for many patients in this study cohort. Regarding the target dose, the SmPC recommends clearly the eventual administration of 200 mg BID as the highest dose, good tolerability provided. Most patients who had a down-titration(12.1%), documented “hypotension” as reason for not up-titrating to the target dose during observation without problem (49.4% of patients with down-titration). The SmPC also recommends (temporary) down-titrations, if hypotension persists despite adjustment of concomitant HF medications. The fact that many patients could not tolerate the target dose raises the question of the real-world applicability of this target dose. A prior analysis has shown for the target dosage to be more effective than lower dosages; however, superiority of S/V over enalapril persisted also for patients on lower doses, respectively (Vardeny, Claggett et al. 2016).

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Conclusion

- The large study population is in line with the expected epidemiology and represents a valid sample of real-world HF patients with reduced ejection fraction and NYHA II-IV in various European countries in an outpatient setting.
- Observance of guideline directed heart-failure medication was suboptimal. Treatment optimization throughout the observational time remained low.
- Patients who were prescribed S/V were slightly younger, had lower LVEF, and a higher disease burden (higher percentage of patients with NYHA class III/IV).
- The most frequently documented S/V treatment regimens were in line with the SmPC and the approved label for S/V. The reduced initial dose of 50 mg BID was used frequently, reflecting the high number of ACEi/ARB-naïve patients who were enrolled and for whom the reduced starting dose is recommended. In many cases, only the reduced target dose of 100 mg BID was achieved.
- The target dose of 200 mg BID was achieved only for around one third of the S/V patients. The majority of the patients who achieved 200 mg BID also maintained the dose for ≥ 12 weeks
- Patients that did not achieve the target dose for S/V were often older (or in the age bracket > 75 years), and had more often NYHA classes III and IV.
- Rates of S/V discontinuation were rather low. The most frequent single reason for S/V treatment discontinuation was hypotension, documented for approximately one fourth of discontinued patients.
- Reported adverse events were mostly comparable to those previously reported in clinical studies. Event rates were lower, which may be explained by the observational study design. Most frequent AEs (by PT) were hypotension (7.9%)

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