

Management of heart failure with reduced ejection fraction in Europe: design of the ARIADNE registry

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Abstract

Aims The introduction of sacubitril/valsartan (an angiotensin receptor–neprilysin inhibitor) is likely to change the approach to the management of patients with chronic heart failure with reduced ejection fraction (HFrEF). The Assessment of Real Life Care–Describing European Heart Failure Management (ARIADNE) registry will evaluate patient characteristics, practice patterns, outcomes, and healthcare resource utilization in the outpatient setting across Europe, with the main focus on factors that guide physicians' decisions to start and continue sacubitril/valsartan in patients with HFrEF.

Methods and results ARIADNE, a prospective, observational registry will enrol 9000 ambulatory patients with HFrEF in 23 European countries Supplement 1. The study will describe 4500 patients treated with conventional treatment (including an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker), and 4500 patients started on sacubitril/valsartan. In each country, patients will be enrolled consecutively over an expected period of 12 months, and followed-up for 12 months. The primary objective is to describe the baseline clinical and demographic characteristics of patients with chronic HFrEF, which guide the decision of the treating physician to initiate sacubitril/valsartan or to continue conventional treatment. A co-primary objective is to identify the baseline characteristics that are associated with the likelihood of reaching the target dose of sacubitril/valsartan 97/103 mg twice daily during follow-up.

Conclusions The ARIADNE registry will provide a comprehensive profile of patients with chronic HFrEF in Europe, will elucidate how management varies between countries, and will help clarify the usage and outcomes associated with use of sacubitril/valsartan in real life.

Keywords Sacubitril/valsartan; ARNI; Heart failure; Implementation; Heart failure with reduced ejection fraction; Real-life data; RASI

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Introduction

The management of chronic heart failure (HF) has markedly improved over the last two decades with the introduction of new diagnostic procedures and pharmacological and device therapies. However, the prognosis of patients with chronic HF remains poor^{1,2} partly because of non-adherence to guideline-based drug therapies by physicians and patients and partly because of poor utilization of existing evidence-based interventions, especially in outpatient settings.^{3–6} The

European Society of Cardiology (ESC) guidelines aim to provide practical, evidence-based recommendations for the diagnosis and treatment of chronic HF across Europe; however, national, regional, and local clinical recommendations as well as health care organization and reimbursement systems vary widely across Europe.

The variation has a significant impact on clinical practice and contributes to the variability in the management of patients with chronic HF.^{4,7–9} In addition, differences exist in the management of patients between primary care and

specialty settings.¹⁰ A more refined understanding of the landscape of chronic HF outpatient management in Europe is hampered by the fact that most large registries have enrolled patients during a hospital stay rather than as outpatients⁴; thus, there is a need for additional real-life data on chronic HF management across Europe.

Adoption of new evidence-based therapies into clinical practice may have tremendous implications for patient outcomes and for healthcare systems. Recently, the ESC and the American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of chronic HF recommended the use of the angiotensin receptor–neprilysin inhibitor sacubitril/valsartan in patients with HF with reduced ejection fraction (HFrEF) with a Class I recommendation.^{11,12} The recommendation was based on the robust findings from the largest Phase III trial conducted in patients with chronic HFrEF [Prospective comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure], in which sacubitril/valsartan was shown to be superior to the ACEI enalapril in reducing mortality [both cardiovascular (CV) and all-cause] and HF hospitalizations.¹³ Although rapid implementation of this novel drug would likely improve outcomes already over a short time span, differences in health systems may cause variable uptake of sacubitril/valsartan across Europe. Hence, it is important to gather additional data on factors that guide physicians' decisions to use sacubitril/valsartan in clinical practice and to describe the association between this drug and clinical outcomes.

Study design and methods

Here we present the study design of the Assessment of Real Life Care–Describing European Heart Failure Management (ARIADNE), a prospective observational non-interventional study.

Study population

Consecutive patients (aged ≥ 18 years) with symptomatic chronic HF (New York Heart Association Classes II–IV) and documented reduced left ventricular ejection fraction assessed by any imaging technique performed at any time in the past and treated by office-based cardiologists or selected primary care physicians (recognized as having special HF interest) are eligible for the study. The following patients will be excluded from the study: those with concomitant or planned participation in any interventional clinical trial; those who are receiving ongoing treatment with sacubitril/valsartan that has been started before market launch in their

respective country (for example, within a clinical trial or early access programme); those who are still within the safety follow-up phase of any previous interventional or non-interventional trial using sacubitril/valsartan, independent of whether they received sacubitril/valsartan or the comparator; those with acute decompensated HF requiring hospitalization at the time of enrolment; or those with existing contraindications according to approved product information. There are no additional restrictions for inclusion or exclusion to ensure that patients in ARIADNE represent the real-world population of patients eligible for sacubitril/valsartan according to the European Medicines Agency label for the drug. The study has ethics approval according to local regulations, and all patients are required to provide written informed consent to participate in the study according to the individual countries' requirements.

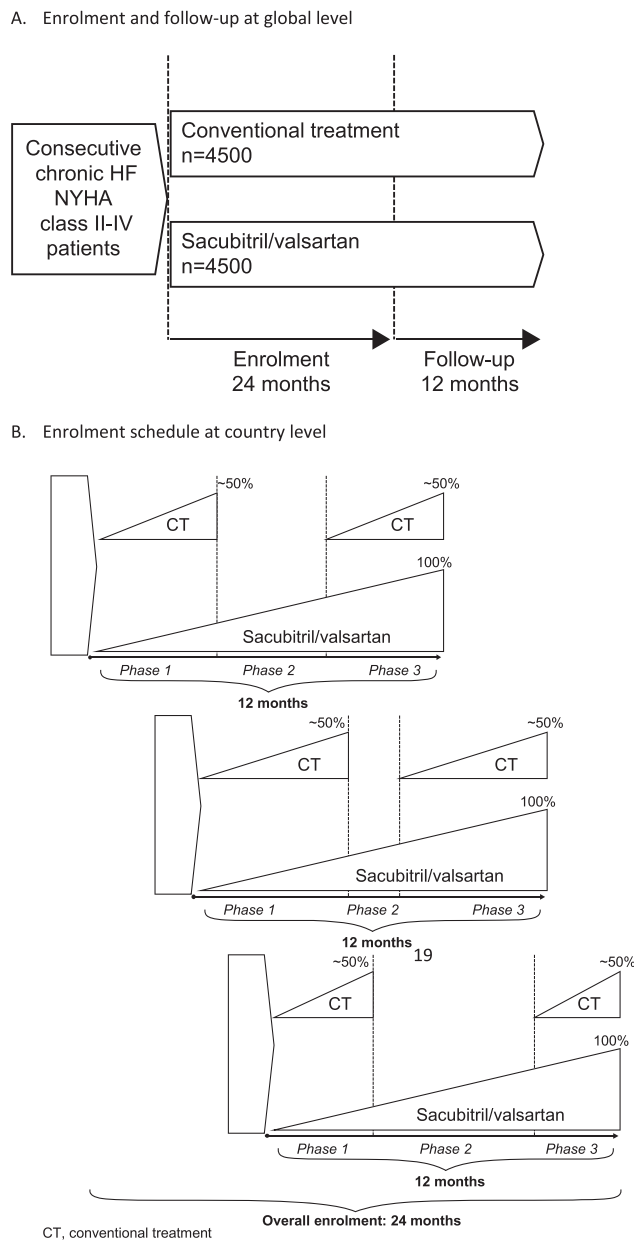
Study design

Data will be collected for two groups of patients with HFrEF: those receiving conventional treatment for chronic HF and those who are being started on, or who are already on, treatment with sacubitril/valsartan. The study will enrol 9000 patients with chronic HFrEF at approximately 1100 sites across 23 European countries, including 4500 patients treated with conventional treatment and 4500 on sacubitril/valsartan. Enrolment will start in each country when sacubitril/valsartan is fully available and reimbursed for clinical use. The participating countries are listed in the Supporting Information.

Assuming that the adoption of sacubitril/valsartan into clinical practice is slow following market authorization and local reimbursement, we expect that it will take longer to enrol patients to the sacubitril/valsartan arm than to the conventional treatment arm. Enrolment at the country level is therefore divided into three phases. There will be continuous enrolment of patients in the sacubitril/valsartan arm throughout the study duration, whereas approximately one-half of the patients in the conventional treatment arm will be enrolled in Phase 1 and the other half during Phase 3 (*Figure 1*). By structuring the patient enrolment in the conventional treatment arm in the two phases, we will observe how the clinical criteria that drive the choice of treatment (conventional treatment vs. sacubitril/valsartan) change over the months following the introduction of sacubitril/valsartan into clinical practice.

The design of the study ensures that there is no impetus for investigators to increase sacubitril/valsartan prescription during Phase 2 of enrolment (when enrolment into the conventional treatment arm is paused). In fact, a patient receiving conventional treatment during enrolment Phase 2 can still participate in the study when enrolment into this group is commenced again (i.e. in Phase 3).

Figure 1 Assessment of Real Life Care—Describing European Heart Failure Management study design: (A) enrolment and follow-up at the global level and (B) enrolment schedule at country level. The enrolment schedule for each country depends on the speed of enrolment in the conventional treatment and sacubitril/valsartan groups. Enrolment in the conventional treatment group is split in two waves, while it is continuous in the sacubitril/valsartan group (Examples A–C). Each country starts enrolment at different timepoints over a 12-month timeframe. In each country, enrolment lasts for 12 months; therefore, at the global level, enrolment will have a continuous pattern that lasts for 24 months. CT, conventional treatment; HF, heart failure; NYHA, New York Heart Association.



Each of the participating countries is expected to have or receive full reimbursement and consequently start the study within approximately 12 months from authorization.

Considering that enrolment will span a maximum of 12 months in each country, enrolment for the entire study is expected to last for 24 months. Enrolment was completed in March 2018, and the last patient will be followed-up to May 2019 (12 months \pm 2 months after enrolment).

The decision to treat a patient with conventional treatment or to start sacubitril/valsartan depends on the clinical judgement of each investigator and is independent of study participation. Patients in either treatment arm can be switched to the alternative therapy at the investigator’s discretion at any time during the study. When the investigator decides to modify a patient’s treatment at any time, the reasons for switching and the details of the new treatment will be documented, i.e. the study will provide information on longitudinal treatment patterns.

The study is designed and shall be implemented and reported in accordance with the guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology 2008, the Strengthening the Reporting of Observational Studies in Epidemiology guidelines¹⁴, and the ethical principles laid down in the Declaration of Helsinki.

Data collection and follow-up

All patients will be followed for 12 months. Follow-up will consist of two visits closest to 6 and 12 months after the baseline visit (recommended visit window of \pm 2 months). No exact date for the second and final visits will be enforced to avoid interference with routine care. If any visit does not occur, the information will be recorded and described as a part of real-world practice. Data variables and the collection schedule are presented in *Tables 1* and *2*, respectively.

Study assessments

The first co-primary descriptive objective of the study is to identify the baseline clinical and demographic characteristics of patients with chronic HFrEF that guide the decision of the treating physician to start sacubitril/valsartan or to continue conventional treatment. A second co-primary objective is to describe the profiles of symptomatic chronic HF patients who are prescribed sacubitril/valsartan and do not achieve and maintain the target dose of 97/103 mg twice daily (BID) within the observation period of 12 months.

Secondary assessments include description of the overall chronic HFrEF population managed in the outpatient setting in Europe in terms of demographics, medical history, comorbidity burden, and previous CV event rate; the proportion of patients achieving and maintaining the target sacubitril/valsartan dose of 97/103 mg BID; the starting dose, titration, and maintenance dose of sacubitril/valsartan in

Table 1 Variables

| Variables |
|---|
| 1. Demographics (age, gender, living at home or institution, relationship status, and education) |
| 2. Medical history and comorbidity burden (with focus on duration of chronic HF, aetiology of chronic HF, last hospitalization for chronic HF, CV conditions and specific comorbidities such as diabetes, renal insufficiency, COPD, anaemia, obesity, and cancer) |
| 3. Clinical events (CV-related and non-CV-related deaths and hospitalizations, myocardial infarction, and cerebrovascular incidents) |
| 4. Number of visits (other than hospitalization) by provider and primary reason during follow-up |
| 5. Diagnostic and therapeutic procedures utilized during follow-up (results will be collected only as available for blood potassium, blood creatinine, BNP and NT-proBNP levels, and for echocardiographic EF. In all other cases, only documentation if the procedure has been performed, along with the primary reason) |
| 6. Treatment received, both pharmacological and non-pharmacological |
| 7. Vital signs and chronic HF signs and symptoms |
| 8. Specifically for sacubitril/valsartan usage: dose at initiation, steps to up-titration, and final dose. In case of lack of up-titration, or down-titration or discontinuation, the reason will be documented |
| 9. EQ-5D and KCCQ: only at those sites where these questionnaires are part of routine management of chronic HF and thus their completion does not affect the non-interventional design of the present study |
| 10. AEs, SAEs, ADRs, and SADR |

AE, adverse event; ADR, adverse drug reaction; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EF, ejection fraction; EQ-5D, 5-dimension Euro Quality of Life Questionnaire; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; SAE, serious adverse event; SADR, serious adverse drug reaction.

Table 2 Data collection schedule

| | Baseline | 6 months ^a | 12 months ^a |
|--|----------------|-----------------------|------------------------|
| Informed consent | X | | |
| Demographics | X | X ^d | X ^d |
| Aetiology of chronic HF | X | | |
| History of chronic HF and CV events | X | | |
| Comorbidities | X | X | X |
| Vital signs, and chronic HF signs and symptoms | X | X | X |
| Diagnostics and therapeutic procedures | X | X | X |
| NT-proBNP (as available) ^b | X | X | X |
| Chronic HF treatment | X ^e | X | X |
| Sacubitril/valsartan dose and titration ^c | X | X | X |
| QoL questionnaires ^b | X | X | X |
| AE/ADR/SAE/SADR | X | X | X |
| Healthcare resource utilization | | X | X |
| End of study assessment | | | X |

AE, adverse event; ADR, adverse drug reaction; CV, cardiovascular; HF, heart failure; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; QoL, quality of life; SAE, serious adverse event; SADR, serious adverse drug reaction.

^aThe recommended visit window should be within ± 2 months of the planned date.

^bOnly at sites where it is part of routine medical management of chronic HF.

^cOnly for patients who receive sacubitril/valsartan.

^dOnly if relevant changes to certain aspects occurred between visits.

^eOnly chronic HF treatment required that is either ongoing at baseline or has been changed within the last 6 months prior to baseline.

patients with different clinical and demographic characteristics; the safety and tolerability of sacubitril/valsartan in the real world; and the conventional treatments (HFrEF drug and non-drug treatments) received by the patients in each participating country (e.g. drug, daily dose, and device therapy) during the course of the study conduct.

In addition, the incidence of chronic HF-related outcomes (death, hospitalizations, adverse events, and major CV events); change in New York Heart Association status; incidence and causes of hospitalizations, doctor visits, and diagnostic procedures; and healthcare resource utilization will be

described, together with a description of baseline health-related quality of life (QoL) and change in QoL scores throughout the observation period (only at those sites where 5-dimension Euro Quality of Life Questionnaire and/or Kansas City Cardiomyopathy Questionnaire QoL questionnaires are part of routine chronic HF management) and a description of baseline BNP/N terminal pro BNP levels and their changes throughout the observation period (only if measurements are available or at those sites where such measurements are part of routine management) in both study groups.

Sample size consideration

With respect to the first main objective, a total of 4500 patients in each group will allow us to estimate patient variables with the following precision: the two-sided 95% confidence interval for qualitative variables (e.g. sex) will be no longer than 3.0% (i.e. estimate \pm 1.5%), and 95% confidence intervals for quantitative variables (e.g. age) will not exceed 6.0%, of the underlying standard deviation (i.e. estimate \pm 0.030 \times standard deviation). In TITRATION, a randomized controlled study,¹⁵ 76% of patients were able to reach and maintain the target dose of sacubitril/valsartan over 12 weeks. However, a higher proportion of patients might be expected to fail up-titration to the target dose in real life because of the absence of a specific titration protocol and lower tolerability. Assuming that the actual lack of up-titration could be as high as two-thirds of all patients, 3000 patients in the sacubitril/valsartan group will form the group for the second co-primary objective.

Data analysis

Continuous data will be expressed as a median with interquartile range (25th to 75th centiles) and categorical data as *n* (%). The factors that are independently associated with treatment choice and achievement and maintenance of target dose of sacubitril/valsartan will be identified via multivariable logistic regression analysis. In addition, factors independently associated with the occurrence of HF-specific clinical events (mortality and hospitalizations) will be analysed via logistic regression or Cox regression, as appropriate. With the exception of treatment choice, the groups will be considered and analysed separately. The subgroups of patients switching from conventional treatment to sacubitril/valsartan will be analysed separately.

The conventional treatment and sacubitril/valsartan groups are expected to differ depending on progressive adoption of sacubitril/valsartan by prescribers; this will be assessed with subgroup analyses within each of the enrolment phases.

Analyses will be performed for the total sample and in subgroups by demographic, clinical, and medical factors (such as sex, duration of HF, renal function, severity of HF, and previous HF treatment). The two groups will not be compared for any efficacy and safety data (the two populations being different by definition).

All statistical analyses will be performed using the Statistical Analysis System (SAS®, Version 9.2 or higher).

Discussion

There is a clear gap between the current guideline recommendations for patients with chronic HF and clinical patient

care.^{16,17} Although guideline recommendations are based on robust clinical evidence, the recommended therapies are not always implemented, are not always prescribed at target doses, and are applied inconsistently across different care settings.^{4,16} ARIADNE is designed to provide a Europe-wide picture of the management of outpatients with chronic HFrEF in real life. It will lead to an understanding of the patterns of usage in, and the possible barriers and disparities to, the adoption of the new drug sacubitril/valsartan.

ARIADNE is the first multinational registry aimed at understanding the management of patients with chronic HFrEF specifically in outpatient settings. It is also the first observational registry following the introduction of new ESC HF guidelines and approval of sacubitril/valsartan. Although several observational registries have recruited patients with HF (Table 3), data from existing registries in Europe provide only limited information on the management of chronic HF for several reasons: poor geographic representation, non-consecutive patient enrolment, limited data in outpatients, insufficient data capture (limited data on healthcare resource utilization and health economics), and lack of long-term follow-up. Most large registries recruit patients from tertiary centres and do not differentiate completely between patients with acute and chronic HF.^{18,31} While the ESC long-term registry aims to describe the clinical epidemiology of outpatients and inpatients with HF across Europe and Mediterranean countries,⁴ several European countries did not enrol patients. Furthermore, registries such as Evidence-Based Treatment HF²⁹ and the ESC HF long-term registry⁴ focused on tertiary care and cardiology centres and therefore may not be representative of the management of European patients with chronic HF by primary care physicians and office-based cardiologists. Registry to Assess Medical Practice with Longitudinal Observation for Treatment HF, an ongoing global HF registry (sponsored by Novartis), aims to include approximately 20 000 patients worldwide including around 2000 patients from Europe.¹⁸ However, patients are enrolled exclusively during hospitalization for HF and data collection is focused on the acute phase with only telephonic follow-up of patients.

Even within outpatient settings, there are differences in the clinical profile and management of patients with chronic HF treated by primary care physicians and office-based cardiologists. The Diagnostic and Therapeutic Methods Used in Patients with Systolic Heart Failure Living in Poland registry in Poland reported that outpatients treated by primary care physicians were older and had more comorbidities than those treated by cardiologists.³² In addition, office-based cardiologists were more likely to use guideline recommended diagnostic and therapeutic interventions than primary care physicians.³² Similarly, in an observational study of chronic HF treatment across 200 primary care centres in Sweden, only 42% of patients received treatment with ACEIs/angiotensin receptor blockers and β blockers; of these, only 20% of patients

Table 3 Overview of other heart failure registries

| Registries | REPORT-HF ¹⁸ | ADHERE ¹⁹ | OPTIMIZE-HF ²⁰ | GWTC-HF ²¹ | EHFS I ²² | EHFS II ²³ | ESC-HF Pilot ⁷ |
|---------------------|---|----------------------|---|-----------------------|----------------------|-----------------------|----------------------------|
| Region/countries | Multinational | USA | USA | USA | Europe ^a | Europe ^b | Europe ^c |
| Condition | Acute HF | Acute HF | Acute HF | HF | HF | Acute HF | HF |
| n | 20 000 (estimated) | 105 388 | 48 612 | 110 621 | 11 327 | 3580 | 5118 |
| Enrolment | Inpatients and post-discharge follow-up | Inpatients | Inpatients and post-discharge follow-up | Inpatients | Inpatients | Inpatients | Outpatients and inpatients |
| Setting | Hospital | Hospital | Hospital | Hospital | Hospital | Hospital | Clinic and hospital |
| Timeframe | 2014–present | 2001–2004 | 2003–2004 | 2005–2010 | 2000–2001 | 2004–2005 | 2009–2010 |
| Data collection | Prospective | Prospective | Prospective | Prospective | Retrospective | Prospective | Prospective |
| PROs | EQ-5D and KCCQ | - | - | - | - | - | - |
| Follow-up | 3 years | - | 60–90 days | - | 12 weeks | - | 1 year |
| Method of follow-up | Telephonic | - | Visit | - | Visit | - | Visit |

ADHERE, Acute Decompensated Heart Failure National Registry; ADHERE-AP, Acute Decompensated Heart Failure National Registry International–Asia Pacific; ALARM-HF, Acute Heart Failure Global Registry of Standard Treatment; ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; ATTEND, Acute Decompensated Heart Failure Syndromes; EHFS I, European Heart Failure Survey I; EHFS II, European Heart Failure Survey II; EQ-5D, 5-dimension Euro Quality of Life Questionnaire; ESC-HF, European Society of Cardiology-Heart Failure; EVITA-HF, Evidence based Treatment in Heart Failure registry; GWTC-HF, Get With The Guidelines-Heart Failure; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure; PROs, patient reported outcomes; SwedeHF, The Swedish Heart Failure Registry; THESUS-HF, The Sub-Saharan Africa Survey of Heart Failure.

^aAustria, Belgium, Czech Republic, Denmark, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Portugal, Russia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, The Netherlands, and UK.

^bAustria, Belgium, Bulgaria, Czech Republic, Denmark, Egypt, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, The Netherlands, Norway, Poland, Portugal, Russia, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, and UK.

^cAustria, France, Denmark, Germany, Greece, Italy, Poland, The Netherlands, Norway, Romania, Spain, and Sweden.

^dAustria, Bosnia Herzegovina, Bulgaria, Czech Republic, Egypt, France, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, and Turkey.

^eAustralia, Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, and Thailand.

^fChina, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand.

^gAustralia, France, Germany, Greece, Italy, Mexico, Spain, Turkey, and UK.

^hCameroon, Ethiopia, Kenya, Mozambique, Nigeria, Senegal, South Africa, Sudan, and Uganda.

Table 3 Overview of other heart failure registries

| Registries | ESC-HF Long-Term Registry ⁴ | ATTEND ²⁴ | ADHERE-AP ²⁵ | ASIAN-HF ²⁶ | ALARM-HF ²⁷ | THEMUS-HF ²⁸ | EVITA-HF ²⁹ | SwedeHF ³⁰ |
|---------------------|--|----------------------|---------------------------|----------------------------|----------------------------|-------------------------|------------------------|---------------------------------|
| Region/countries | Europe ^d | Japan | Asia-Pacific ^e | Asia-Pacific ^f | Multinational ^g | Africa ^h | Germany | Sweden |
| Condition | HF | Acute HF | Acute HF | Acute HF | Acute HF | Acute HF | HF | HF |
| n | 12 440 | 4842 | 10,171 | 8000 (estimated) | 4953 | 1006 | 1853 | 75 000 (estimated) |
| Enrolment | Outpatients and inpatients | Inpatients | Inpatients | Outpatients and inpatients | Inpatients | Inpatients | Inpatients | Outpatients and inpatients |
| Setting | Clinic and hospital | Hospital | Hospital | Clinic and hospital | Hospital | Hospital | Hospital | Clinic and hospital |
| Timeframe | 2011–2013 | 2007–2011 | 2006–2008 | 2013–present | 2006–2007 | 2007–2010 | 2009–2011 | 2000–present |
| Data collection | Prospective | Prospective | Retrospective | Prospective | Retrospective | Prospective | Prospective | Prospective |
| PROs | - | - | - | KCCQ | - | - | - | EQ-5D |
| Follow-up | - | - | - | 3 years | - | 6 months | 1 year | Automatic monthly, indefinitely |
| Method of follow-up | - | - | - | Visit | - | Visit | Telephonic/contact | Linking to population registry |

were receiving $\geq 50\%$ of the dose recommended in the the ESC guidelines.³³ Interestingly, a collaborative approach between primary care physicians and cardiologists led to higher rates of treatment optimization and adherence to guideline-recommended therapy.³⁴

Accordingly, an ongoing low-interventional study—Prospective Evaluation of Natriuretic Peptide Based Referral of Cardiac HF Patients in Primary Care—is evaluating whether N terminal pro BNP level-guided referral of patients with chronic HF to a cardiologist will be associated with treatment optimization in patients managed in primary care. The ARIADNE registry focuses on understanding the management of outpatients with chronic HF by office-based cardiologists and selected primary care physicians who are recognized as HF specialists. Data from these studies will provide unique opportunities for designing quality improvement initiatives to optimize clinical care of patients with chronic HF across primary care and specialty settings.

Sacubitril/valsartan is the first therapy shown to be superior to the standard-of-care ACEI enalapril for the treatment of HFrEF in many years. ARIADNE will lead to an insight into the decision-making of office-based specialists as to how sacubitril/valsartan is used in the individual patients they see as compared with conventional treatment. ARIADNE will also show how that decision-making changes over time.

Potential limitations of ARIADNE are typical of a non-interventional study, where no stipulation regarding data collection can be made. Not all recruiting sites use QoL questionnaires or all of the laboratory variables in their routine management of chronic HF; and thus, these data will not be available for all patients. In addition, there is no randomization or blinding in a non-interventional study and so QoL data in particular will need to be interpreted cautiously. However, the non-interventional nature of the study is the only way to obtain real-life data. In order to obtain a representative sample of patients with chronic HF, ARIADNE will neither mandate diagnostic nor therapeutic processes that would distort recruitment or management during follow-up. The inclusion criteria require that each patient has documentation of reduced left ventricular ejection fraction in the past through any imaging technique to make sure that only patients potentially eligible for sacubitril valsartan are included.

The lack of stipulations regarding potentially confounding factors, such as duration of conventional treatment, duration of chronic HF, prior treatments, and disease severity, are further potential limitations. Such limitations are typical for non-interventional studies, which aim to assess the real-life situation where the enrolled population *per se* is not homogeneous, and a certain homogeneity can only be achieved by adequate and medically justified stratification and sub-grouping prior to analysis and not through stringent inclusion criteria.

Conclusions

ARIADNE aims to meet the need for a Europe-wide observational registry that will enhance the understanding of the management of patients with chronic HFrEF in the outpatient setting. It will give clarity for physicians on the introduction, usage, and effects of sacubitril/valsartan in real life. In addition, ARIADNE will help in assessing adherence to guideline recommendations in outpatient settings and enable future design and conduct of quality improvement initiatives.

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Conflict of interest

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Supporting information

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

Data S1. Participating countries.

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