The PARADIGM-HF trial was published in September 2014. The combination of sacubitril plus valsartan (SAC/VAL) at a fixed dose was demonstrated to be superior to enalapril in reducing the risk of death or admission for heart failure (HF). Based on the results of this trial, SAC/VAL was approved for the treatment of chronic heart failure (CHF) in July 2015 (USA) and November 2015 (EU). This paper reviews the design of the PARADIGM-HF trial, the results obtained for efficacy and safety, and the trial’s most relevant limitations. Should SAC/VAL replace standard treatment with angiotensin-converting-enzyme inhibitors (ACE inhibitor) or angiotensin-II-receptor blockers (ARB) as recommended by the PARADIGM-HF investigators? Overestimation of the benefits and underestimation of the harms associated with SAC/VAL limit the external validity of the efficacy and safety results of PARADIGM-HF. Limitations of the study include a stronger inhibition of the Renin-Angiotensin-Aldosterone System (RAAS) in the SAC/VAL arm, early trial stopping for benefit, and the use of multiple strict inclusion and exclusion criteria. Variables such as age, sex, functional class and co-morbidities of patients in the double-blind trial do not match those of standard patients with CHF who receive ambulatory or hospital-based treatment in real life. SAC/VAL should only be used in patients with a very specific profile, similar to those for whom efficacy and safety have been demonstrated. SAC/VAL cannot be considered a first-choice therapy for CHF.
Heart failure: epidemiological and clinical relevance
Heart failure (HF) is a common health problem in developed countries that affects 1-2% of the adult population\(^1\) and up to 10% of the population greater than 70 years of age\(^2\). According to the PRICE study\(^3\), the prevalence of HF in the Spanish population older than 45 years is 6.8%, with no gender-based differences. Prevalence increases with age and reaches 16% above age 75. HF prevalence is increasing due to population ageing and increased survival rates of patients after acute events of ischemic heart disease. No data are available on the prevalence of HF in Navarre, Spain, but the HF diagnosis-related group (DRG) 127 accounted for 1.5% of admissions (fifth most common cause of hospitalization), with a mean hospital stay of 7.3 days\(^4\). According to the Instituto de Salud Pública de Navarra\(^5\), mortality associated with HF accounted for 2.8% of all deaths in men and 4.2% in women in 2013. The MAGGIC meta-analysis\(^6\) compiled prognostic data from 39,372 patients with HF and showed that 40.2% died within 2.5 years of first admission for heart failure. The growing prevalence and high mortality related to HF have raised great hopes for the development of new therapies such as sacubitril/valsartan (SAC/VAL).

Sacubitril/valsartan: mechanism of action and place in therapeutics
Mechanism of action
Sacubitril blocks the breakdown of natriuretic peptides (NP) in patients with HF thereby causing long-term compensatory effects\(^7\). By inhibiting neprilysin, sacubitril causes an increase in NP plasma concentrations and activity, with beneficial effects for patients. Yet, neprilysin also degrades angiotensin II, an important mediator of the development and progression of HF. Neprilysin inhibition by sacubitril leads to an increase in angiotensin II, which activates the Renin-Angiotensin-Aldosterone System (RAAS)\(^8\). Therefore, sacubitril alone is not effective in the treatment of HF and could even be harmful if RAAS is not simultaneously blocked. Neprilysin inhibition is only beneficial when the RAAS is also inhibited. This is why sacubitril is used in combination with valsartan.

The PARADIGM-HF trial: design and main results
Main Research Question
Is the SAC/VAL combination more effective, equally effective, or less effective than enalapril in reducing mortality or hospitalization for heart failure?

Design
PARADIGM-HF\(^1\) was a multinational, randomized, double-blind, phase III trial financed by Novartis. A total of 8,399 patients (SAC/VAL: 4,187; enalapril: 4,212) were included.
Patients

Inclusion criteria were: age ≥ 18 years, diagnosis of CHF with reduced LVEF (≤ 40% subsequently lowered to ≤ 35%), absence of HF symptoms (New York Heart Association (NYHA) classification II-IV), elevated NP plasma levels, current therapy with ACE inhibitors or ARB and beta-blockers (except if contraindicated).

Phases of the trial

Figure 1 displays the flow of patients across the three phases of the trial, namely: selection, run-in, and double-blind treatment period. The initial sample was composed of 18,071 eligible patients with CHF-REF. The protocol established five criteria for inclusion and 23 criteria for exclusion, which caused 41.7% of initial candidates to be excluded. In total, 62% of exclusions were for insufficiently elevated NP levels, 19% for hyperkalemia and 5.5% for kidney failure. Once the selection phase was completed and prior to randomization, a run-in period started. A total of 10,513 patients were included in this phase. These patients had to stop their current therapy with ACE inhibitors or ARB and entered a run-in period with simple masking. First, patients received enalapril (10 mg BID) for a median of 15 days. After this treatment, 10.5% of patients were excluded. After a 36-h washout, the patients who were not excluded received SAC/VAL for a median of 29 days, with dose escalation (SAC/VAL 100 mg BID up to 200 mg BID). After the run-in period with SAC/VAL, 10.4% of patients were excluded. Thus, almost 20% of patients initially deemed eligible were excluded from the controlled trial. More than half were excluded due to adverse effects, without any observed differences between enalapril vs. SAC/VAL in the occurrence of severe adverse events (hypotension, hyperkalemia and renal dysfunction). The remaining 8,442 patients who completed the run-in phase were randomized to the double-blind treatment period. After randomization, six patients were excluded due to inappropriate randomization, and 37 for bad clinical practice. Finally, 8,399 patients (46.5% of the 18,071 initial candidates) were considered eligible for the assessment of efficacy.

Intervention

The 8,399 final candidates were randomized to the double-blind treatment period. The SAC/VAL group (n=4,187) received SAC/VAL 200 mg BID. Controls (n=4,212) received enalapril 10mg BID. The two groups also received standard treatment (beta-blockers, aldosterone inhibitors, among others).

Outcome Measures

The primary endpoint was death from cardiovascular disease (CV) or admission for HF. The components of the primary endpoint were CV death and first admission for HF. The secondary endpoint was all-cause mortality.

Results

SAC/VAL was superior to enalapril in reducing the absolute risk of CV death or death from HF (21.8% vs. 26.5%), with a number needed to treat (NNT) of 21, a 95% confidence interval (95%CI) of 15 to 31, and a hazard ratio (HR) of 0.80 (95%CI: 0.73 to 0.87). All data correspond to the median follow-up (27 months). Both components of the primary endpoint contributed to the reduction of risk. The effect was maintained along the follow-up period and was consistent across all subgroups. All-cause mortality decreased by 2.8% in the SAC/VAL group as compared with the enalapril group (17.0% vs. 19.8%) for a HR of 0.84 (95%CI: 0.76 to 0.93).

Authors’ conclusions

SAC/VAL was superior to enalapril in reducing the risk of mortality and hospital admission for heart failure.

Threats to the external validity of the results of the PARADIGM-HF trial

Did the profile of study patients match that of standard patients treated in clinical practice?

At the moment of randomization, the mean age of patients was 63.8 years (51% were younger than 65 years and 19% had an age of 75 years or more), with predominance of male patients (78%)13. In total, 70.5% of patients fell within NYHA Class II, 24.0% within Class III, 4.6% within Class I (despite inclusion criteria), 0.7% within Class IV.

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A. Brain natriuretic peptide (BNP) ≥150 pg/ml or Serum N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) ≥600 pg/ml if the patient had not been hospitalized for HF in the last year; or BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml if the patient had been hospitalized for HF in the last year.
Figure 1. PARADIGM-HF trial. Flow-chart.

18,071 patients with CHF-REF screened for enrolment

SELECTION

41.7%

10,513 patients
RUN-IN PHASE

ENALAPRIL
10 mg BID

10.5%

WASHING OUT

Sac/val 100 BID
Sac/val 200 BID

10.4%

8,442 patients
RANDOMIZATION

8,399

4,187
sac/val

4,212
enalapril

41.7% patients excluded for not meeting inclusion criteria:
- 62% not meeting minimum levels NP
- 19% having serum K ≥ 5.2 mmol/L
- 5.5% having eGFR < 30 mL/min/1.73m2

20% patients excluded for:
- Adverse event: 55%
- Abnormal laboratory or other test result: 6%
- Protocol deviation, administrative problem or lost to follow-up: 14%
- Death: 5%
- Other reason: 8%

43 patients excluded for:
- Invalid randomization: 6
- Violations Good Clinical Practice: 37
and functional class was unknown in 0.2% of patients. Therefore, based on their functional NYHA Class, 75.1% of patients had mild heart failure (Classes I and II). In 2005, the PRICE study revealed that 44% of Spanish patients with HF were male (78% in the PARADIGM-HF trial). Based on data from this study and from the Instituto Nacional de Estadística, it is estimated that there were 1,174,394 patients with CHF in Spain in 2005, of whom 46% were 75 years of age or older, and 27% were younger than 65 (19% and 51%, respectively, in the PARADIGM-HF trial). This mismatch is not unique to the PARADIGM-HF trial; older patients are usually underrepresented in trials on HF.

Does SAC/VAL reduce the risk of hospital admission for typical Spanish patients with HF? In PARADIGM-HF, the age of patients included in the double-blind phase whose risk of admission for HF was reduced does not match that of standard patients hospitalized for HF in Spain. According to a report on SAC/VAL by the Spanish Society of Hospital Pharmacy, 82% of patients admitted for HF (regardless of their EF) were between 70 to 94 years of age, with mean age between 80 to 84 years according to different studies.

The age of PARADIGM-HF patients was almost 20 years younger, at 63.8 years. It is almost certainly easier to reduce the risk of hospitalization for HF in patients who are relatively young and stable – as in PARADIGM-HF with 75.1% of patients in NYHA Class I/II – than in older patients with more comorbidities, more advanced and unstable heart disease.

Two epidemiological studies on CHF have been performed in Spain in patients treated in different units (primary care, internal medicine, geriatrics or cardiology). The patients who most closely matched PARADIGM-HF patients were those treated in cardiology units. This is consistent with the profile of patients described in the BADAPIO and Card-CHUS trials, in which patients treated in cardiology units where predominantly relatively young men with a reduced EF.

In summary, the age, sex, NYHA functional class and comorbidities of patients included in the double-blind phase of PARADIGM-HF were not typical of patients with CHF receiving outpatient or hospital-based treatment in Spain.

More than 70% of patients included in the double-blind study had hypertension

Following the selection and run-in periods, the population remaining for the double-blind treatment period in PARADIGM-HF was so strictly selected that their age was significantly below that of standard patients with CHF who are regularly treated in outpatient and inpatient units. Surprisingly, despite the relatively young age of patients included in the double-blind phase of PARADIGM-HF, the prevalence of hypertension in this sample was abnormally high (>70%). As reported by the authors, PARADIGM-HF was designed to select patients who best tolerated the target dose of enalapril and, especially, of SAC/VAL, given that hypotension was the most relevant clinical concern with use of SAC/VAL. Hypotension (symptomatic or not) was an exclusion criterion in the selection and run-in phase. As a result, the proportion of patients with hypertension included in the double-blind study exceeded 70%. The proportion of patients with hypertension included in the enalapril arm of the CONSENSUS trial was 24%. Prevalence of hypertension among Spanish patients with CHF treated in outpatient cardiology units – the population that most closely matches patients included in the PARADIGM-HF double-blind study – ranges from 54 to 56%.

Was enalapril the appropriate comparator?

Despite the existing evidence on the efficacy of ARB in reducing mortality in these patients, ACE inhibitors have been proven to be superior (especially enalapril). Thus, ARB are recommended only for patients who show intolerance to ACE inhibitors (generally due to cough). In relation to the reduction of mortality in these patients, Dr Milton Packer – one of the primary investigators of PARADIGM-HF – justified the decision to use enalapril versus SAC/VAL: “Because angiotensin receptor blockers (ARB) have not been shown to reduce the risk of death in patients with heart failure, they were not used as the comparator”.

If an ARB had been used (valsartan, for example), the theoretical benefit of sacubitril could have been isolated. As the new drug is not SAC/VAL but sacubitril, the burden of proof should have relied on the clinical benefit of sacubitril. Yet, the PARADIGM-HF trial does not provide any direct evidence on the effects of sacubitril. A new trial sponsored by Novartis (PARAGON-HF) is underway to compare SAC/VAL with valsartan.

APPARENTLY, THE PATIENTS IN THE SAC/VAL GROUP RECEIVED A MORE INTENSE TREATMENT THAN ENALAPRIL PATIENTS

B. CONSENSUS (1987) was the first study to demonstrate that an ACE inhibitor (enalapril) could reduce all-cause mortality from 52% to 36%. The study sample was composed of 127 patients with severe CHF (NYHA IV). The duration of treatment was 12 months and the dose of enalapril was 20 mg BID (relative risk reduction was 31%).
in patients aged > 50 with CHF and conserved LVEF (≥ 45%). A similar comparison in PARADIGM-HF would have been more informative, given that many patients with CHF-REF receive ARB (theoretically due to intolerance to ACE-inhibitors). In Spain, the proportion of patients with CHF-REF treated with ARB in outpatient cardiology units reaches 29%. Therefore, if the effects of SAC/VAL are to be compared with the standard treatment, enalapril was the best comparator. In contrast, if the goal is to identify the added benefit of sacubitril, SAC/VAL should be compared with valsartan.

Dosing

The target dose of enalapril in PARADIGM-HF was 10 mg BID. The protocol did not allow for this dose to be exceeded. This is half the dose recommended in SEC guidelines (20 mg BID) and is the minimum dose recommended in USA guidelines (10 to 20 mg BID). However, the target dose of valsartan matched that recommended in European and American guidelines (160 mg BID). The bioavailability of valsartan in combination with sacubitril is greater than that of valsartan alone, which means that the 103 mg dose used as the target dose in PARADIGM-HF is equivalent to the 160 mg daily dose of standard therapy. Dr. Packer states that the mean dose of enalapril in his trial matched that used in the most relevant trials previously performed, which demonstrated that enalapril reduced mortality. Yet, it is possible that aiming for a target dose of 20 mg BID depending on patient tolerance would have improved experimental results in the enalapril arm.

There is evidence that a considerable proportion of the study patients could have tolerated an enalapril dose of 20 mg BID. In CONSENSUS trial, the proportion of patients with hypertension included in the enrolled arm was 24% (>70% in PARADIGM-HF) and 22% of patients reached the enalapril target dose of 20 mg BID (0% in PARADIGM-HF). Is the recommended dose of enalapril met in real world practice? A study on the adequacy of the SEC guidelines for patients with CHF treated in outpatient cardiology units of 27 Spanish hospitals sheds light on this question. 22% of patients who had completed dose titration reached ACE inhibitor target dose, the same proportion as in CONSENSUS. If we also consider patients in the titration phase, the percentage is reduced to 16%. This occurs with 56% of patients with hypertension. If these percentages are obtained in real life, it can be thought that they could be even higher in the PARADIGM-HF trial in which more than 70% of the patients included in the double blind are hypertensive.

The authors did not provide a plausible explanation for not allowing patients with good tolerance to receive a dose of 10 to 20 mg of enalapril BID, thereby failing to follow standard cardiologic recommendations. In contrast, the recommended dose of valsartan was administered in this trial. This is striking, given that Dr. McMurray -the principal investigator of PARADIGM-HF- is one of the main coordinators of the SEC guide for HF.

Was the degree of RAAS inhibition the same in the two arms of the study?

According to Dr. Packer, it was. “The renin-angiotensin system was inhibited to a similar degree in the 2 treatment arms; thus, any difference was related to the inhibition of nephrilysin by sacubitril/valsartan.” Yet, three lines of evidence contradict this statement. First, the dose of valsartan was proportionally higher than that of enalapril. Second, sacubitril inhibits RAAS indirectly which would “help” valsartan block RAAS. Third, the unusually high incidence of cough in the SAC/VAL arm (according to ACE inhibitors range) suggests that RAAS inhibition in this arm of the study was greater than that caused by valsartan.

One of the beneficial effects of increased natriuretic peptide (NP) concentrations on heart structure and function in patients with CHF is RAAS inhibition. In fact, the NP system is considered a “natural antagonist” of RAAS, as it inhibits this system by reducing the secretion of renin and aldosterone. The inhibition of nephrilysin by sacubitril causes an increase in NP levels. Some authors emphasize this effect when describing the action of SAC/VAL.

C. For example, we can achieve a reduction to half the average consumption (“average dose”) of cigarettes in a given population of smokers through two interventions: a) reducing cigarette consumption by half in each and every one of the smokers without that none stop smoking, and b) reducing by half and at random the number of smokers in said population. With both interventions the average consumption (the “average dose”) of cigarettes would be reduced by half but with the “b” we would get, in addition, a relevant reduction (of 50%) in the number of smokers. Probably, the greatest benefit in public health (the greatest added benefit) would be obtained with this last intervention. With the treatment of ICC-FER with enalapril, the same thing happens: the greatest added benefit would be obtained by taking each patient the maximum dose of enalapril that is tolerated without exceeding 20 mg twice a day.
RAAS inhibitors are known to cause cough. Cough is more severe when associated with ACE inhibitors, but also occurs with ARB and aliskiren. In relation to enalapril, coughing is reported as a very frequent adverse effect (≥1/10). However, it is reported as a rare adverse effect of valsartan and aliskiren (≥1/1000 to < 1/100). Cough is reported as a frequent adverse effect of SAC/VAL (≥1/100 to < 1/10) and affected 11.3% of subjects in the SAC/VAL arm in PARADIGM-HF, very close to the 14.3% incidence of cough reported for the enalapril arm. Based on trials comparing ACE inhibitors with valsartan, Novartis recently reported that the probability of cough with ACE inhibitors was 7.9% vs. 2.6% for valsartan. In a trial enrolling 129 patients who experienced cough with ACE inhibitors, cough was reduced to 20% when they were switched to valsartan. In the same report, Novartis notes that the percentage of patients who discontinued treatment due to cough in the VALIANT trial was 0.6% for valsartan vs. 2.5% for captopril. A review on the safety of valsartan revealed that the incidence of cough was 4 to 6 times higher with enalapril than with valsartan, and 8 times higher with lisinopril than with valsartan, whereas the incidence of cough associated with valsartan has been reported to be the same as with placebo. That cough incidence in the SAC/VAL arm of PARADIGM-HF (11.3%) fell within ACE range (≥1/10) and close to the 14.3% observed with enalapril. This suggests that RAAS inhibition by valsartan was reinforced in the SAC/VAL arm. Additionally, in the light of the doses administered, ACE inhibition was probably more intense in the SAC/VAL arm than in the enalapril arm.

More intense inhibition of the RAAS in the SAC/VAL arm than in the enalapril arm of PARADIGM-HF may explain the striking occurrence of hypotension (symptomatic or not) in the SAC/VAL arm both during the run-in period and the double-blind period. This could also explain why SAC/VAL patients had a mean systolic blood pressure that was 3.2 mmHg lower than those in the enalapril arm at 8 months follow-up.

Other limitations to the validity of the trial

Run-in period

The run-in period reduces the probability that patients with drug intolerance are included in the double-blind period. This reduces the external validity of safety and efficacy results, even though the intention-to-treat approach is adopted for analysis. Performing a run-in period to exclude patients with drug intolerance leads to an overestimation of the benefits and an underestimation of the harms of the treatment. In addition, the design of the run-in period was not the same for the two drug arms. Why was dose escalation used with SAC/VAL but not with enalapril? Why was the run-in started with enalapril but not with SAC/VAL, or not randomly assigned? Are these aspects irrelevant when the two drugs cause the same severe adverse events (hypotension, hyperkalemia and kidney dysfunction)? It is arguable that the safety and efficacy results obtained in PARADIGM-HF could have been different had the run-in been performed conversely, that is, with first exposure to SAC/VAL, starting with the target dose from baseline for 15 days (no dose escalation phase) followed by a dose-escalation phase for enalapril over 29 days. Also, when the effects of the high rate of drop-outs occurred in the run-in period (=20%) were assessed during the analysis of sensitivity, the investigators suggested that the effect size of drop-outs on the primary endpoint could narrow the apparent difference between SAC/VAL and enalapril to from 20% to 15-16%, although statistical and clinical significance was maintained.

Stopping the trial early for benefit

The PARADIGM-HF was stopped early after a median follow-up duration of 27 months. Early termination is considered to be justified by the substantial reduction observed in the risk of hospitalization and death. It has been reported that when a trial is stopped early, results can be overestimated by a mean of 30%. This phenomenon limits the external validity of efficacy results.

Finally, 14.8% of the patients included in the double-blind period were treated with a defibrillator/implantable cardioverter, and 6.8% received biventricular stimulation (resynchronization therapy), whereas the reported proportion of patients treated with these therapies in Europe is almost double. These technologies have been demonstrated to reduce death and disability in patients with CHF-REF. If the frequency of use of these devices had been similar to that in real practice, the number of CV events might have been lower. In consequence, the magnitude of the differences observed and the probability that they reached statistical significance might have decreased. As a result, the benefits of the study therapy would have been mitigated.

What kind of patients would be most suited to treatment with SAC/VAL?

Based on trial criteria and theoretical premises, the proportion of CHF-REF patients eligible for SAC/VAL would be low. This is confirmed by experience in real practice, which yields a proportion of eligible patients ranging from 11.4 to 21%. Patients are prescribed new
drugs when symptomatic response to standard therapy is inappropriate. This strategy may not be appropriate in the case of SAC/VAL. Poor response to standard therapy at the recommended dose was not one of the inclusion criteria for the PARADIGM-HF trial. Indeed, almost 75% of patients remained asymptomatic or presented only mild symptoms of congestive heart failure (NYHA I/II) at randomization.

In total, 53.5% (n=9,672) of the 18,071 initial candidates with CHF-REF were not included in the double-blind phase. PARADIGM-HF only reports the epidemiological and clinical profile of the patients included in the double-blind phase; the profile of patients excluded is unknown. The only data provided are that some patients were excluded for presenting insufficiently elevated NP levels, comorbidities or abnormal lab results in the screening phase, or for occurrence of adverse events or abnormal lab results in the run-in period. Data on the profile of patients who responded to SAC/VAL are as important as data on patients whose response to SAC/VAL is unknown. In fact, sub-group analysis revealed a significant correlation between baseline functional status and a greater effect on the primary endpoint in patients with mild disease (NYHA I/II) as compared to those with severe disease (NYHA III/IV) ($p = 0.03$). Therefore, data should have been provided to describe differences between the included and excluded patients for variables such as age, sex and NYHA class, EF, NP level and important comorbidities.

Use of sacubitril/valsartan in Navarre

Figure 2 shows the number of patients treated with SAC/VAL prescribed by physicians of the Public Health System of Navarre between January and August 2017. Data source: Database on drug use of the Navarre Health Service. During this period, the number of patients prescribed SAC/VAL increased five-fold from 29 in January to 144 in August. Mean age was 76.7 years (men 75.2, women 79.7) and 68% were male. The relatively advanced age of these Spanish patients, compared with those studied in PARADIGM-HF (mean age...), may suggest that SAC/VAL is being prescribed inappropriately, including to patients with more comorbidities and more advanced and instable disease than the patients in PARADIGM-HF.

Figure 2. Number of patients treated with sac/val in Navarre. Period January-August 2017. National Health System prescriptions.

Source: Prescription database of the Navarre Health Service.
Conclusions

As PARADIGM-HF did not isolate the effect of sacubitril, it is unknown if the intensity of RAAS inhibition was similar in the two study arms (enalapril 20 mg/d vs SAC/VAL).

There is evidence that RAAS inhibition was stronger in the SAC/VAL arm. This could at least partially explain the differences obtained. Differences in RAAS inhibition would be the result of using a proportionally higher dose of valsartan than of enalapril in addition to the effect of sacubitril on RAAS inhibition.

Benefits of SAC/VAL may be overestimated while harms may be underestimated by PARADIGM-HF. Other limitations to the external validity of this trial include early trial stopping for benefit and the use of strict and numerous inclusion and exclusion criteria.

Variables such as age, sex, functional class and comorbidities of patients in the double-blind trial do not match those of patients with CHF who receive outpatient or hospital-based treatment, notably in Spain. Applying PARADIGM-HF inclusion and exclusion criteria, a low proportion of CHF-REF patients would be eligible for SAC/VAL therapy in real world practice.

The above considerations should constrain the use of SAC/VAL, and imply it should not be used as first-choice therapy for most patients with CHF-REF. At present, SAC/VAL should be used in a specific population of patients similar to those in whom its efficacy and safety have been demonstrated. In other words, SAC/VAL should only be administered to patients whose clinical and epidemiological profile is similar to that of the patients included in the double-blind phase of the PARADIGM-HF trial. In Spain, the patients with CHF-REF who most closely matched PARADIGM-HF patients are those treated in outpatient cardiology units.
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