Sacubitril-Valsartan for Heart Failure with Reduced Left Ventricular Ejection Fraction: A Retrospective Study

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Abstract

Introduction In sacubitril-valsartan (sacub/v), the effects of an angiotensin II receptor blocker (ARB) exerted by valsartan are strengthened by the addition of sacubitril, an inhibitor of neutral endopeptidases. PARADIGM - HF study proved this association to be superior to enalapril in

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reducing both all-cause death and cardiovascular mortality, as well as heart failure (HF) hospitalizations in patients with cardiac insufficiency and reduced left ventricular ejection fraction(HFREF) belonging to NYHA class II-IV. To test whether even in our experience sacub/v is associated with favorable outcomes concerning mortality and morbidity, an outpatient small population of HFREF patients was retrospectively studied, of whom one third was treated with sacub/v instead of conventional therapy with ACE -inhibitors or ARBs.

Methods A retrospective cohort study was carried out to assess the effects of sacub/v in addition to beta-blocker and mineral receptor antagonist (MRA) in a group of HFREF patients in NYHA classes II-III compared with conventional therapy (comprising ACE inhibitor or ARB added to beta-blocker plus a MRA) administered in a second group of HFREF patients with comparable clinical features retrospectively enrolled as controls. In the two groups, the therapeutic regimen was established in accordance with the preferences of the treating physician. Additionally, in both groups, evidence-based drug therapy was supplemented by the adjunct of a loop diuretic, usually furosemide, at variable doses. The primary outcomes of interest were all-cause death and HF hospitalizations. Safety outcomes were symptomatic hypotension, angioedema, hyperkalemia and worsening renal function.

Results Mortality at six months was 6.8% in patients under therapy with sacub/v versus 34% in those treated with conventional therapy (odds ratio[OR] = 0.14; 95% CI: 0.04-0.49). Moreover, HF hospitalizations in the observation period considered were 4.5% in sacub/v group versus 59% in the conventional therapy group (OR = 0.03; 95% CI: 0.01-0.14). Safety outcomes included in our study (angioedema, hyperkalemia, hypotension and worsening renal function) showed a comparable profile in the two groups, with evidence of good tolerability of sacub/v , except for the side - effect " hypotension" (PAS <100 mm Hg) , found in 15.9% of patients under sacub/v versus 5.7% reported in controls(OR=3.14; 95% CI: 0.94-10.55).

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Conclusions In our experience, sacub/v has yielded a strong protection against both all-cause death and HF hospitalizations at six months , in the absence of significant noxious side effects. Nevertheless, considering the retrospective character of the study and the relatively exiguous sample size, further post marketing observational studies would be desirable . In particular, studies aiming at exploring safety of the new pharmacologic principle, namely mainly focusing on hypotension and angioedema, are warranted, in order to validate further this very efficacious molecule for therapy of chronic HF, especially stable HFREF in NYHA classes II-III.

Key words: sacubitril valsartan; heart failure; treatment

MANUSCRIPT

Background The introduction of sacubitril-valsartan into the officially approved therapeutic

repertoire for chronic heart failure (CHF) has been carried out in Italy only on March 12, 2017. Indeed, only since this date, the drug in question, in its various dosage formulations, has received by the competent regulatory authority the official authorization for reimbursement by the Italian National Health Service(1). In the present study we have provided the preliminary data derived from our usage of sacubitril- valsartan, i.e., those concerning the first 8 months of our experience with this drug in the CHF setting. The study was designed as a retrospective cohort study. In fact, it has mainly aimed at investigating some aspects of pharmaco-epidemiology, and has   primarily addressed at describing elements and acquisitions derived from the experience achieved by our group. Thus, references to acquisitions from other research groups or other Centres devoted to treatment of heart failure are reported in the text in a quite essential and synthetic manner. Indeed, it's our intention to perform a wider and more detailed examination of the issues related to the use of this drug   in a next narrative review.

Materials and methods

Patients' selection. The drug was administered, at the discretion of the treating physician, in CHF patients who had various degrees of compromise of hemodynamic and clinical status (Class II or III NYHA). In accordance with the instructions provided by the societal guidelines (2), NYHA IV patients were excluded from the treatment. Therapy was implemented considering some of the operating models applied by the PARADIGM –HF (3   ) study. In our case-record, patients assigned to therapy with sacubitril-valsartan, all of whom had an ascertained   diagnosis of CHF dating back at least a year, had to have a history of previous use of inhibitors of the renin-angiotensin-aldosterone system(RAAS), maintained for at least three months. In particular, in all of the patients admitted to therapy with sacubitril-valsartan a   therapy with ACE- inhibitor or angiotensin-receptor antagonist (ARB) had   been   already practiced, regardless of clinical outcomes (clinical improvement, or alternatively, unaltered or worsening outcome). Moreover, the patient had to be free from a possible history of angioedema (either related to the use of ACE inhibitors or arisen without any identifiable iatrogenic cause). The vast majority of patients who had been admitted to sacubitril-valsartan therapy had already been undergoing a treatment with evidence-based medications,labeled 1A according to the recent (January 2016) European Heart Failure Guidelines(4), that is, an association comprising a) a beta-blocker   (carvedilol or metoprolol or bisoprolol or nebivolol), b) an ACE inhibitor or ARB   and   c) a mineralcorticoid receptor antagonist (MRA) selected from the following: spironolactone, eplerenone, canrenone or potassium canrenoate. This association was supplemented by the regular use of a loop diuretic (furosemide or torsemide), given at variable time intervals according to specific patient's clinical picture.

However, the pre-existence of a comprehensive and multi-target, evidence-based therapy for CHF treatment was not considered a binding requirement for the implementation of sacubitril-

valsartan therapy. Indeed, inclusion criteria were: a condition of NYHA class II-III; a history of prior ACE- inhibitor or ARB therapy with enalapril dose no less than 10 mg daily or equivalent dosage of another ACE- inhibitor or ARB; the absence of previous episodes (one or more) of angioedema; the absence of hypotension, defined by a systolic blood pressure level of ≤ 100 mmHg; the absence of severe chronic renal failure (defined by an estimated glomerular filtration rate [GFR],calculated by the Modified Diet in Renal Diseases[MDRD](5)method, no less than 30 ml/min/1.73 m2), or severe hepatic insufficiency, malignant neoplasia or anemia. Unlike the Paradigm-HF study, the fact of overcoming a well-defined threshold-value of NT-proBNP (e.g., 600 pg/ml) was deemed not necessary in order to regard the patient eligible for treatment with sacubitril-valsartan. Under these conditions, patients with hemodynamic or clinical destabilization (acute heart failure) or patients who had never been treated with ACE-i or ARBs were not admitted to therapy with sacubitril-valsartan. Moreover, during the aforementioned innovative regimen, administration of ACE-i or ARBs or aliskiren was deemed contra-indicated (risk of   effect summation). Conversely, in patients treated with sacubitril valsartan, MRA administration was not forbidden. Likewise, beta-blockers were kept except for the possible cases of new, super-imposed complications judged to be contraindications to persistence of pharmacologic beta-blockade. **.** In addition, depending on the view of the treating physician, a switch from one treatment to another was allowed, but in this case, according to the intention-to-treat principle, the final statistical calculations were performed considering the patient as belonging to treatment group originally assigned.

Modalities adopted for administration of the   evidence- based drugs as well as for sacubitril-valsartan

Target doses to be reached within a reasonably short period of time in the conventional therapy group were to be the following: for beta-blockers, a target dose was established depending on the

employed molecule (for carvedilol, 25 mg twice daily, for bisoprolol 5 mg twice daily and for nebivolol 5 mg once a day). Likewise, for ACE-inhibitors, the daily target dose was 20 mg for enalapril, 10 mg for ramipril and 20 mg for lisinopril. As an alternative to ACE inhibitors, the use of ARBs was provided for, with a daily target dose of 225 mg for irbesartan, 100 mg for losartan and 160 mg for valsartan. In addition, for MRAs, a daily target dose of 75 mg for spironolactone and 50 mg for both canrenone and eplerenone was established.

Up-titration of sacubitril-valsartan was carried out provided that in any candidate patient the following measures were accomplished: regular measurements(twice weekly) of systolic blood pressure and periodic determinations(every two months) of serum electrolytes (in particular serum potassium and sodium), serum creatinine and related GFR, whose calculation being obtained using MDRD equation, as well as periodic determinations(every two months) of transaminases, serum NT- proBNP and Hb. The usual criterion was to start assigning to patient 24 + 26 mg of sacubitril-valsartan twice daily ; subsequently, he had to be transferred to dosage of 49 + 51 mg of sacubitril- valsartan twice daily on day 14th, except for cases of obvious intolerance (e.g., symptomatic hypotension, hyperkalemia,etc). Then, after a further 14 days, only in patients with good hemodynamic adaptation and clinical tolerance, the recommended target dose of 97 + 103 mg of sacubitril –valsartan was provided for, to be assumed once again twice daily.

Study design

A retrospective cohort study was undertaken by the authors, all of whom were cardiologists with expertise in pharmacoepidemiology who were not directly involved in the therapeutic management of patients undergoing sacubitril-valsartan . Nevertheless, according to the dictates of hospital directorate, they were allowed to have full access to clinical, echocardiographic and hematochemical data of the investigated patients. In collecting data of patients treated with sacubitril- valsartan and those instead undergoing conventional therapy, attention was paid to

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protect patients' privacy as well as to ensure scrupulous preservation of their anonymity. The

data from the files of   telematic archives were stored on pendrives and later used for the

evaluation of the outcomes of interest explored with the aid of statistical programs.

Outcomes of interest.
The main purpose of the study was the retrospective evaluation of the impact of therapy

 with sacubitril- valsartan compared with the conventional regimen on the primary endpoints a)

all- cause death and b) heart failure hospitalization. Secondary outcomes were the need to

increase by at least 25%   the weekly dose of loop diuretic and impairment by no more than 4

percentage points of the left ventricular ejection fraction. Safety outcomes were: symptomatic

hypotension, angioedema, hyperkalemia (serum K+ > 5.5 mEq/L) and worsening renal function

(increase in serum creatinine > 0.3 mg/dl).

Statistical analysis
Anthropometric, clinical, anamnestic, haematochemical and echocardiographic data in the 2

groups, the one treated with sacubitril-valsartan and the other subjected to conventional therapy

were compared using unpaired samples T test in order to compare the continuous variables. Chi

square test with Yates equation was used instead for comparison of dichotomous variables;

when needed, Fisher's exact test was adopted for dichotomous variables.

For some binary outcome variables (death at 6 months, heart failure hospitalization, need for

diuretic dose increase, LVEF deterioration at 6 months, symptomatic hypotension) comparison

between patients exposed and not exposed to sacubitril valsartan was conducted by employing

the 2x2 contingency tables with calculation of the rough (unadjusted) odds ratio and its 95%

confidence interval.

Cox proportional hazards regression analysis   was used to calculate the association of some

exposure variables, including the use of sacubitril- valsartan, with the risks of death,

hospitalization, increased diuretic dose and worsening   LVEF in the course of therapy. Kaplan

Meier curves were built to estimate with the log-rank test the possible statistical significance of the difference in mortality and hospitalizations found by comparing   patients exposed and those not exposed to sacubitril-valsartan.

Results

Our experience with sacubitril-valsartan was necessarily short ,namely no longer than 6 months, given that the marketing of sacubitril-valsartan in reimbursable form by the Italian National Health Service started only in March 2017. Patients who, according to discretionary view of the attending physician, were assigned to conventional treatment, i.e., combination therapy including beta-blockers, ACE-inhibitors or ARBs plus MRAs, had a profile of anthropometric, clinical and echocardiographic features marked by very strong similarities   (see Table 1) with those shown by patients assigned to sacubitril valsartan.

Altogether, 132 patients were included in the retrospective study. The mean duration of chronic heart failure treatment in our retrospective study was 5 ± 1.14 months (mean ± standard deviation). Patients assigned to sacubitril valsartan in addition to beta-blocker and MRA were 44, of whom 22 female , whereas the group assigned to conventional therapy with ACE-inhibitors or ARBs in addition to beta-blockers and MRAs consisted of 88 patients, of whom 43 were female.

The proportions of patients achieving the target dose in each group were evaluated: for   beta-blockers considered on the whole, the target- dose, i.e., the dose regarded as desirable target at the end of an appropriate up-titration period , was reached in 75% of cases; for ACE-inhibitors the target dose was reached in 90% of cases, for ARBs as well as for MRAs in 100% of cases.

Moreover,for sacubitril valsartan, the target dose was achieved in 80% of cases.

In patients treated with sacubitril/valsartan, a very important reduction in both all-cause mortality and   heart failure hospitalizations was found, in comparison with those subjected to traditional

therapy. In fact, mortality was 6.8% in patients under therapy with sacubitril/valsartan versus 34% in those undergoing conventional therapy (OR = 0.14; 95% CI: 0.04-0.49)(Table 2 and Fig 1).

Heart failure hospitalizations in the observation period considered were 4.5% in sacubitril/valsartan group versus 59% in the conventional therapy group (OR = 0.03; 95% CI: 0.01-0.14)

(Table 3 and Fig 1). Also the need to increase diuretic dose in the sacubitril/valsartan group was less frequent: 9% versus 56.8% (OR: 0.08; 95% CI: 0.03-0.23)(Table 4 and Fig 1) . Conversely, a deterioration of no more than 4 percentage points of LVEF was very similar in the two groups : 68.2 versus 62.5% (nonsignificant OR of 1.29; 95% CI: 0.60-2.77)(Table 5 and Fig 1).

Safety outcomes included in our study (angioedema, hyperkalaemia, hypotension and worsening renal function) showed a comparable profile in the two groups(Fig 2), with evidence of good tolerability of sacubitril/valsartan, except for the side – effect " hypotension" (PAS <100 mm Hg) , found in 15.9% of patients under sacubitril/valsartan versus 5.7% reported in controls(Table 6 and Fig 2).

With multivariate Cox proportional hazards regression analysis, use of sacubitril/valsartan has been shown to be a protective factor against the death at 6 months (hazard ratio (HR) = 0.132; 95% CI: 0.0396 to 0.4454; p = 0.0011) (table 7) with a predictive value greater than that has been exhibited by the age or serum NTproBNP , which both have proved to be risk factors for death at 6 months.

In addition, by means of Cox proportional hazards regression analysis, therapy with sacubitril valsartan has been shown to be associated with decreased risk of heart failure hospitalizations (HR = 0.0677; 95% CI: 0.0161 to 0.2845, p = 0.003) (table 8).

Discussion

The truly innovative value of sacubitril/valsartan consists in the fact that it is the first commercially available drug in which the activity of angiotensin receptor blocker(ARB) is favorably integrated and complemented by the combination with a drug, namely sacubitril, capable of enhancing the vasodilator, anti-adrenergic and anti-apoptotic properties   possessed by the natriuretic peptide system as well as its action antagonizing the inappropriate rises in ventricular filling pressures. So far, in chronic heart failure, therapeutic activity had focused on the blockade of some neuro-hormonal systems rather than on the enhancement of the hormonal activity of the peptidergic cardiovascular system, i.e., the cardioprotective system primarily centered around the effects of the B-type natriuretic peptide and atrial natriuretic peptide.

More in detail, it is known that in the setting of volume expansion or pressure overload, the resulting wall stress promotes synthesis of pre-proB-type natriuretic peptide (pre-proBNP) in the ventricular myocardium (6). Subsequently, the peptide is cleaved first to proBNP, then to the biologically active B-type natriuretic peptide (BNP) and the inactive fragment, amino-terminal (NT)-proBNP (7). It is also known that the release of BNP induces improved myocardial relaxation and plays an important regulatory role in response to acute increases in ventricular volume by antagonizing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin–angiotensin–aldosterone system (RAAS) [8].

Nevertheless, it was found that the favorable vasodilatory and natriuretic properties of natriuretic peptides(NPs) are not sufficient to counteract the noxious effect of RAAS hyperactivation in a significant percentage of cases (8). Thus, the signaling function regarding hemodynamic imbalance, as exerted by NPs when massively secreted, has been judged more important than their possible role in the effective counterbalance against the vasoconstrictive and sodium-retentive systems (8).

However, some important elements should be emphasized to explain the substantial ineffectiveness of the natriuretic peptide system as a counterweight to the activation of the adrenergic system and RAAS. In particular, the destroying and rapid molecular degradation of BNP, which is carried out by a type of neutral endopeptidase known as neprilysin, makes the functions exercised by BNP rather ephemeral and of overall modest significance. In this regard, it may be useful to underline here that already 15 years ago several attempts were made using inhibitors of neutral endopeptydases, in particular omapatrilat (9) in order to prolong the half-life of natriuretic peptides(BNP and ANP) and thus achieve an enhancement of their counter-regulating effects, primarily consisting in lowering ventricular filling pressures and promoting diuresis and natriuresis, so as to antagonize sympatho-adrenergic system and RAAS.

There are some analogies in the structure and pharmacodynamic properties of omapatrilat , and sacubitril, the latter being part of the sacubitril-valsartan molecule. Sacubitril is really a prodrug that is activated to sacubitrilat (LBQ657) by de- ethylation via esterases(10). Sacubitrilat inhibits the enzyme neprilysin (10) which is responsible for the degradation of both atrial and B-type natriuretic peptides.

However neprilysin also catalyzes the degradation process of several other peptides, including bradykinin, a flogosis mediator whose massive release can cause vasodilation, angioedema, and airway obstruction. This concomitant blockade of bradykinin degradation has, however, proved to be much more intense and dangerous when it is associated to use of omapatrilat compared to sacubitril-valsartan .

In fact, in the past, omapatrilat, when was being used as investigational drug, caused relatively numerous cases of severe angioedema involving the glottis with obstruction of the first airways (9). Therefore, safety concerns mainly related to the high incidence of iatrogenic angioedema

concurred to prevent omapatrilat from being validated by the FDA as a therapeutic agent for cardiac failure. Furthermore, omapatrilat was not found to be superior to enalapril in improving the primary end point of death and hospitalization for heart failure (9).

Conversely, for sacubril-valsartan, based on the safety data of PARADIGM HF(3), the incidence of angioedema was 0.5%, as opposed to a 0.2% incidence observed in patients treated with the enalapril used as comparator. Therefore, the acceptable impact of this collateral effect with the sacubitril has made it possible to remove the important safety concerns , which had previously led the regulatory authorities to deny the entrance of omapatrilat in the market.

As regards the efficacy outcomes, PARADIGM HF(3) has reported superiority of sacubitril valsartan compared with enalapril, since the new drug has reduced the risk of cardiovascular death and HF hospitalization (composite endpoint) by 21.8% with respect to 26.5% found in patients treated with enalapril. Sudden death was reduced by 20% compared to the enalapril (HR: 0.80; p = 0.0082). Moreover, death for irreversible progressive heart failure was reduced by 21% in in the patients treated with sacubitril/valsartan compared to patients treated with enalapril (HR: 0.79; p = 0.0338).

In our retrospective study, we were unable to distinguish the cases of exitus depending on the mode (whether sudden or due to progressively worsening failure). Moreover our data ,since they have been calculated from a non-randomized observational study, are burdened by the risk of bias, for example, confounding by indication. Based on our data, we can affirm that sacubitril/valsartan has given a strong protection against both the death at six months (OR: 0.14; 95% CI 0.04-0.49) and HF hospitalizations (OR: 0.03; 95% CI: 0.01-0.14).The abovementioned logistic regression results(tables 2-3 and Fig 1) are also largely confirmed by the multivariate Cox proportional hazards regression analysis(table 7 and 8)

Study limitations

The main limitations of the study are the small sample size and the "case-control" study design.

Indeed, a major characteristic of case-control studies is that data on potential risk factors

are collected retrospectively and as a result may give rise to bias.

Conclusions

Based on our data, **sacubitril valsartan has conferred a strong protection against both the death at six months and HF hospitalizations, in the absence of significant harmful side effects**. Nevertheless, considering the retrospective character of the study and the relatively small sample size, further post-marketing observational studies are warranted . In particular studies exploring safety of the new pharmacologic principle, e.g., studies centered about the risks of angioedema and hypotension, are required, in order to validate further this very efficacious molecule for treatment of CHF, especially stable cardiac decompensation in NYHA class II-III.

References

1)Khder Y , Shi V , McMurray JJV , Lefkowitz MP . Sacubitril/Valsartan (LCZ696) in Heart Failure Handb Exp Pharmacol. 2017;243:133-165.

2) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical PracticeGuidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-1488.

3)McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004

4) Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975

5)Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999 Mar 16;130(6):461-70

6)Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J. 1998 May;135(5 Pt 1):825-32.

7) Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, Nishino K, Yoshimasa T, Nakao K. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. J Clin Invest. 1995 Sep;96(3):1280-7.

8) Maisel A, Mueller C, Adams K Jr et al State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail 2008; 10:824–839

9) Packer M , Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002 Aug 20;106(8):920-6.

10) Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). J Clin Pharmacol 2010 Apr;50(4):401-14.

Fig1 **Effects of sacubitril-valsartan**

Study or Subgroup	Sacubitril-valsartan		Control		Weight	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95 % CI
	Events	Total	Events	Total			
angioedema	0	44	1	88	1.0%	0.66 [0.03, 16.42]	
death	3	44	30	88	18.1%	0.14 [0.04, 0.49]	
hospitalizations	2	44	52	88	32.1%	0.03 [0.01, 0.14]	
hyperkaliemia	2	44	5	88	3.1%	0.79 [0.15, 4.25]	
hypotension	7	44	5	88	2.7%	3.14 [0.94, 10.55]	
Increase in diuretic dosing	4	44	50	88	29.4%	0.08 [0.03, 0.23]	
increase in serum creatinine	2	44	4	88	2.5%	1.00 [0.18, 5.68]	
LVEF deterioration	30	44	55	88	11.3%	1.29 [0.60, 2.77]	
Total (95% CI)		352		704	100.0%	**0.34 [0.24, 0.50]**	
Total events	50		202				

Heterogeneity: Chi^2 = 45.34, df = 7 (P < 0.00001); I^2 = 85%

Test for overall effect: Z = 5.59 (P < 0.00001)

Odds Ratio scale: 0.001 0.1 1 10 1000
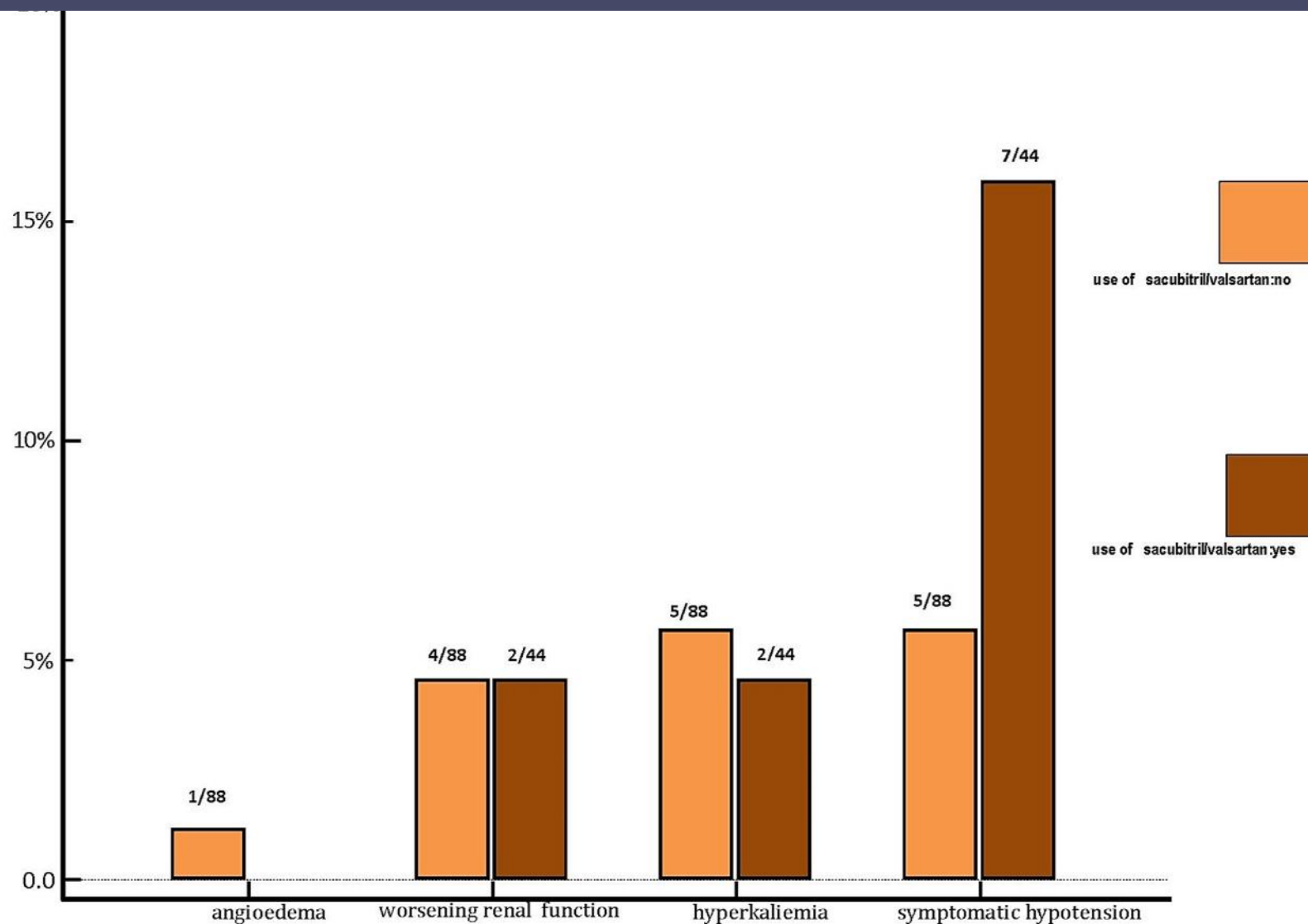Favours sacub-valsartan   Favours control

Figure 2 Distribution of side effects (angioedema, worsening renal function, hyperkalemia and symptomatic hypotension) within the population of retrospectively studied CHF patients (no.132) with percentage calculation of cases occurring in subjects treated (No. 44) and in those untreated (no.88) with sacubitril / valsartan.

Legend: CHF, chronic heart failure; worsening renal function: any increase of ≥ 0.3 mg/dl in serum creatinine compared to baseline

Comparison of demographics and clinical, laboratory, and echocardiographic features of patients examined in the retrospective study according to whether or not a CHF patient was treated with

	Patients (no. 44) treated with sacubitril valsartan	Patients (no. 88) treated with conventional therapy, i.e., ACEI or ARBs (without sacubitril-valsartan)	*p*-Value
Baseline Demographics			
Age (years, mean ± SD)	76 ±5.5	75 ± 7.5	0.4341
Male sex % (*n*)	70.5% (31)	68.2% (60)	0,9470
BMI on admission (Kg/m^2, mean ± SD)	28.2 ± 6.87	27.2 ± 5	0.3427
Heart rate at the first visit (beats/min, mean ± SD)	90 ± 19	85 ± 20	0.1711
Heart rate after six months (beats/min,mean ± SD)	64± 18	80±20	**< 0.0001**
SBP at the first visit (mmHg, mean ± SD)	115 ± 26	125 ± 30	0.0617
SBP after six months (mmHg, mean ± SD)	110 ± 21	115 ± 18	0.1574
Comorbidities			
Ischemic etiology of HF % (*n*)	45.4% (20)	45.4% (40)	0.8529
Valvular etiology of HF % (*n*)	15.9 % (7)	17 % (15)	0.9342
CMP-induced HF % (*n*)	27.2% (12)	30.6% (27)	0.8396
Other cause of HF % (*n*)	11.3% (5)	6.8% (6)	0,5179
Atrial fibrillation % (*n*)	**50% (22)**	**25 % (22)**	**0.0074**
CABG % (*n*)	22.7% (10)	34% (25)	0.2550
History of hypertension % (*n*)	56.8% (25)	52.2 % (46)	0.7576
DM on insulin % (*n*)	22.7% (10)	28.4% (25)	0.6255
COPD % (*n*)	11.3% (5)	12.5% (11)	1.0000
ICD % (*n*)	9% (4)	10.2 % (9)	1.0000
NYHA class IV at baseline % (*n*)	2.2% (1)	6.8% (6)	0.4234
Hematochemical Variables			
NT-proBNP at the first visit (pg/mL, mean ± SD)	800.84 ± 123	756.22 ± 129	0.0594
NT-proBNP after 6 months (pg/mL, mean ± SD)	290.5 ± 90.1	591.47 ± 213.81	**< 0.0001**
Serum creatinine (mL/dL, mean ± SD)	1.46 ± 0.55	1.6 ± 0.4	0.0981
Serum Na$^+$ at the first visit (mEq/L, mean ± SD)	136± 1.55	137± 2.5	**0.0166**
Serum Na$^+$ after 6 months (mEq/L, mean ± SD)	138.5 ± 10	138.4 ± 8.6	0.9526
Serum K$^+$ at the first visit(meq/L, mean ± SD)	4.5± 0,6	4.7± 0.9	0.1851
Serum K$^+$ after 6 months (meq/L, mean ± SD)	4.8 ± 0.65	4.1 ± 0.85	**< 0.0001**
Echocardiographic data at the first visit			
LVEF % (mean ± SD)	38.2 ± 6	37 ± 5.5	0.2538

LVESD (mm, mean ± SD)	58 ± 10	59 ± 14	0.6733
E/A ratio (mean ± SD)	3 ± 1.25	3.4 ± 1.35	0.1026
Deceleration time (ms, mean ± SD)	136 ± 22	145 ± 25	**0.0362**

Legend SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; CABG: coronary artery bypass graft; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter

		Death over a six- month FU		
		yes	no	
Sacubitril- valsartan	yes	3	41	44
	no	30	58	88
	TOTAL	33	99	132

	Point estimate	95% confidence interval	
		lower	upper
Odds ratio (cross product)	**0.1415**	**0.0404**	**0.4949**

p **(Fisher exact test) = 0.000516**

Table 2 The odds of death were significantly lower in patients with chronic heart failure who were taking sacubitril - valsartan (44 patients on the whole) in addition to beta-blocker and MRA compared to patients treated with conventional therapy (88 patients on the whole), who were taking ACE-inhibitor or ARB in addition to beta-blocker and MRA. Therefore, sacubitril- valsartan has exerted a more favorable effect on mortality compared to conventional therapy with ACE- inhibitor or ARB .

Legend: FU, follow-up; ACE, angiotensin-converting enzyme; MRA, mineral-corticoid receptor antagonist; ARB, angiotensin receptor blocker

sacubitril valsartan		heart failure hospitalizations		
		yes	no	Total
	yes	2	42	44
	no	52	36	88
	Total	54	78	132

	Point estimate	95% confidence interval	
		lower	upper
Odds ratio (cross product)	**0.0330**	**0.0075**	**0.1449**

p (Fisher exact test) < 0.000001

Table 3   The odds of hospitalization were significantly lower in patients with chronic heart failure who were taking sacubitril - valsartan (44 patients on the whole) in addition to beta-blocker and MRA compared to patients treated with conventional therapy (88 patients on the whole), who were taking ACE-inhibitor or ARB in addition to beta-blocker and MRA. Therefore, sacubitril- valsartan has prevented hospitalization more efficaciously than conventional therapy with ACE- inhibitor or ARB .

Legend: ACE, angiotensin-converting enzyme; MRA, mineralcorticoid receptor antagonist; ARB, angiotensin receptor blocker

		Increase in loop diuretic dosing over a six- month FU		
		yes	no	Total
Sacubitril-valsartan	yes	4	40	44
Sacubitril-valsartan	no	50	38	88
	Total	54	78	132

	Point estimate	95% confidence interval	
		lower	upper
Odds Ratio (cross product) =	0.0760	0.0250	0.2308

p **(Fisher exact test) <0.0001**

Table 4 The odds of an increase in doses of ≥ 25 % of loop diuretic (furosemide or torsemide) with respect to initial dose were significantly lower in patients with chronic heart failure who were taking sacubitril - valsartan (44 patients on the whole) in addition to beta-blocker and MRA compared to patients treated with conventional therapy (88 patients on the whole), who were taking ACE-inhibitor or ARB in addition to beta-blocker and MRA. Therefore, the use of sacubitril- valsartan has resulted in a less frequent need of diuretic dose augmentation during follow-up compared to conventional therapy with ACE- inhibitor or ARB .

Legend: FU, follow-up; ACE, angiotensin-converting enzyme; MRA, mineral-corticoid receptor antagonist; ARB, angiotensin receptor blocker

		Slight deterioration of LVEF over a six month FU		
		yes	no	Total
Sacubitril-valsartan	**yes**	30	14	44
	no	55	33	88
	Total	85	47	132

	Point estimate	95% confidence interval lower	upper
Odds Ratio (cross product)	**1.2857**	**0.5969**	**2.7693**

p (chi- square corrected according Yates)= 0.65280

Table 5 In patients with chronic heart failure who were taking sacubitril - valsartan (44 patients on the whole) in addition to beta-blocker and MRA, the odds of a slight deterioration (no more than 4%) of LVEF over a six-month follow-up did not differ from those of patients treated with conventional therapy (88 patients on the whole), who were taking ACE-inhibitor or ARB in addition to beta-blocker and MRA. Therefore, the use of sacubitril- valsartan did not yield a significant advantage in protecting left ventricle against progressive enlargement due to underlying heart disease, compared to conventional therapy with ACE- inhibitor or ARB .

Legend: LVEF, left ventricular ejection fraction; FU, follow-up; ACE, angiotensin-converting enzyme; MRA, mineral-corticoid receptor antagonist; ARB, angiotensin receptor blocker

		symptomatic hypotension		
		yes	**no**	**Total**
Sacubitril-valsartan	**yes**	7	37	44
	no	5	83	88
	Total	12	120	132

	Point	95% confidence interval	
	estimate	lower	upper
Odds ratio (cross product) =	3.1405	0.9353 -	10.5454

p **(Fisher exact test)** $= 0.10361$

Table 6 In patients with chronic heart failure who were taking sacubitril - valsartan in addition to beta-blocker and MRA, a nonsignificant trend(p=0.103) toward an increased frequency of symptomatic hypotension was detected with respect to patients undergone conventional therapy with ACE-inhibitor(or alternatively ARB), beta-blocker and MRA. Please see also the text.

Legend: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRA, mineral-corticoid receptor antagonist

Survival time	Duration of treatment(months)
Endpoint	death at 6 months

Variable	coefficient	st. error	hazard ratio	95% CI		p
Atrial fibrillation	0.3974	0.4485	1.4879	0.6206 to 3.5677		0.3756
age	0.05737	0.01919	**1.0590**	**1.0201 to 1.0994**		**0.0028***
sacubitril-valsartan	-2.0185	0.6203	**0.1329**	**0.0396 to 0.4454**		**0.0011***
NT-proBNP	0.001425	0.0005435	**1.0014**	**1.0004 to 1.0025**		**0.0087***
LVEF at entrance	-0.01904	0.02506	0.9811	0.9344 to 1.0303		0.4474

Table 7 Outcome variable: death at 6 months**. Exposure variables:** atrial fibrillation (dichotomous)**;** age (continuous)**;** therapy with sacubitril-valsartan (dichotomous); serum NT-proBNP (continuous); LVEF at entrance (continuous).

Legend: NT-proBNP, N-terminal pro b-type natriuretic peptide; LVEF, left ventricular ejection fraction
*= p-value which attains statistical significance, i.e., $p < 0.05$

Survival time	duration of treatment (months)
Endpoint	**heart failure hospitalizations**

Variable	coefficient	Std. error	hazard ratio	95% CI	*p*
Atrial fibrillation	-0.1910	0.4105	0.8261	0.3710 to 1.8392	0.6416
age	0.01814	0.01438	1.0183	0.9901 to 1.0473	0.2072
NT-proBNP	0.0002895	0.0004971	1.003	0.9993 to 1.0013	0.5604
Sacubitril-valsartan	-2.6931	0.7364	**0.0677**	**0.0161 to 0.2845**	**0.003***
LVEF at entrance	0.04061	0.02188	1.0414	0.9980 to 1.0868	0.0634

Table 8 Outcome variable: heart failure hospitalizations**. Exposure variables:** atrial fibrillation (dichotomous)**;** age (continuous)**;** serum NT-proBNP (continuous)**;** therapy with sacubitril-valsartan (dichotomous); LVEF at entrance (continuous).

Legend: NT-proBNP, N-terminal pro b-type natriuretic peptide; LVEF, left ventricular ejection fraction   *= *p*-value which attains statistical significance, i.e., *p* <0.05