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RESEARCH ARTICLE

Early Administration of Sacubitril/Valsartan is Associated with more Rapid NT-proBNP Recovery in High-Risk Patients Hospitalized for Acute Heart Failure

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ABSTRACT

BACKGROUND: in patients hospitalized for heart failure with reduced ejection fraction (HFrEF), randomized controlled trials have demonstrated some advantages in starting sacubitril/valsartan before discharge. However, information about the effects of sacubitril/valsartan use in the acute phase of HfrEF hospitalizations is limited.

AIM: To evaluate clinical, biomarker, and echocardiographic effects of starting sacubitril/valsartan in real-world HFrEF patients before discharge. METHODS: retrospective analysis of 124 consecutive patients (58.9% males, 75.6±11.4 years) hospitalized for HFrEF. In 36, sacubitril/valsartan was started before discharge (Group A); in the remaining 88, at the 1-month follow-up visit (Group B). The primary endpoint was time-averaged NT-proBNP level reduction from admission to discharge. RESULTS: Group A showed a worse baseline clinical risk profile (diabetes: 47.2 vs. 20.7%, p=0.007; coronary artery disease: 66.7 vs. 22.7%, p<0.001; systolic blood pressure: 118.0±20.8 vs. 132.9±22.9 mmHg, p=0.001; left ventricular ejection fraction: 28.5±5.5 vs. 32.1±7.6%, p<0.0004). Nevertheless, the time-averaged mean NT-proBNP reduction was significantly higher in group A patients (ratio of change -0.30, 95% CI -0.40 to -0.21, <0.0001 vs. group B). Creatinine and K^+ levels did not change significantly during the hospital stay. Multivariate analysis suggested diabetes, coronary artery disease, higher systolic blood pressure, and the need for inotropic support as independent predictors for in-hospital sacubitril/valsartan treatment.

CONCLUSIONS: in real-world patients, starting sacubitril/valsartan in-hospital rather than waiting for further stabilization was associated with a more considerable reduction of NT-proBNP levels at discharge, with an excellent safety profile. These data confirm randomized trials results, extending them to higher-risk real-world HFrEF patients.

Keywords: sacubitril/valsartan; ARNI; acute heart failure; heart failure therapy

Introduction

In the PARADIGM-HF study, the angiotensin-receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (SV) was superior to angiotensin-converting enzyme (ACE) inhibitors in decreasing both mortality and hospitalization rates in symptomatic patients with heart failure and depressed left ventricular ejection fraction (HFrEF)[1]. However, in PARADIGM-HF, only clinically stable patients in therapy with ACE inhibitors for at least four weeks were eligible for the study; therefore, in the PARADIGM-HF population, SV was never started during hospitalization for acute heart failure (HF). However, the first weeks following discharge are critical for patients hospitalized for acute HF[2-4]. Thus earlier ARNI administration without waiting for formal clinical stabilization has been advocated[4, 5] and accepted in current guidelines[6]. SV administration before or immediately after discharge in patients hospitalized for HFrEF has been proven feasible and safe in the randomized controlled trial (RCT) TRANSITION[7]. Furthermore, in the RCT PIONEER-HF, an earlier start of ARNI during hospitalization for HF has been shown to provide clinical benefits in terms of a more rapid reduction of NT-proBNP levels and prevention of early rehospitalization for HF[8].

Unfortunately, besides TRANSITION and PIONEER-HF, few small clinical studies evaluated in-hospital SV treatment in patients with acute HF[9-15], sometimes with conflicting results.

Therefore we decided to retrospectively evaluate a real-world population of patients hospitalized for acute decompensated HFrEF, comparing patients treated with SV during hospitalization with those scheduled for starting the drug as outpatients four weeks after discharge.

Methods

Population

We performed a retrospective analysis of a cohort of patients consecutively admitted for acute HFrEF from January to December 2019 to the Cardiology Division of our Institution (Joint Hospitals of the Verbano-Cusio-Ossola District, Piedmont, Italy). We limited the observation to 2019 to avoid a possible bias from the COVID-19 pandemic effects[16]. The definition of acute HF fulfilled the more recent international guidelines[6]. We excluded patients with the following:

1) acute coronary syndrome, uncorrected primary valvular heart disease, active myocarditis, and obstructive, hypertrophic, or restrictive cardiomyopathy;
2) a history of cancer with exposure to mediastinal radiotherapy or systemic chemotherapy in the last year;
3) active treatment with SV at the moment of hospital admission;
4) end-stage organ damage with severely compromised life expectancy;
6) specific contraindications to ACE inhibitors or SV therapy (end-stage renal disease, angioedema, previous adverse reactions to ACE inhibitors);
7) age <18 years old;
8) pregnancy in the last year.

According to the timing of SV therapy start, we divided this population into two groups:

1) Group A, patients who started SV during their hospital stay.
2) Group B, patients scheduled for starting SV as outpatients at least four weeks after discharge.

The two groups' follow-up was evaluated on an intention-to-treat basis.

Outcomes

As the primary efficacy outcome, we considered the proportional time-averaged change in the NT-proBNP concentration from baseline to discharge, calculated as in the PIONEER-HF trial[17] (the average NT-proBNP values at discharge divided by the average value at baseline).

As secondary efficacy outcomes, we included the proportional change in the left ventricular ejection fraction (LVEF) from baseline through 1-month follow-up, 1-month all-cause mortality, and 1-month readmission rates for acute HF.

As secondary safety outcomes, we evaluated the occurrence of worsening renal function (defined as an increase in the serum creatinine concentration of ≥0.5 mg per deciliter [≥44 μmol per liter] or a decrease in the estimated glomerular filtration rate of ≥25%), clinically relevant hyperkalemia (defined as a serum potassium concentration of ≥5.5 mmol per liter), symptomatic hypotension (defined as mean arterial pressure < 90mmHg with symptoms) and angioedema.

In-hospital Sacubitril Valsartan treatment

The choice to start SV therapy during the hospital stay or on an outpatient basis was made at the caring clinicians' discretion. Hemodynamic stability, the pre-requisite for the in-hospital start of SV, was defined as the presence of each of the following conditions: 1) systolic blood pressure ≥100 mm Hg; 2) stable intravenous diuretic dose and no intravenous vasodilator use during the previous six hours 3) no use of intravenous inotropes during the previous 24 hours.

The initial SV dose was administered orally twice daily, with dosing based on the systolic

blood pressure and according to the algorithm of the PIONEER-HF study [8]. SV therapy was up-titrated during the hospital stay to the maximum dose tolerated.

Outpatient Sacubitril Valsartan treatment

Patients scheduled for SV starting after discharge received an ACEi or ARB for at least four weeks and then switched to SV. After 24 hours of washout from ACEi or ARB, patients have initially prescribed either 24 mg of sacubitril with 26 mg of valsartan, and SV was then up-titrated to the maximally tolerated dose during the subsequent outpatient visits. Fig. 1 summarises the study protocol with the flow chart of patient follow-up.

Laboratory Methods

Venous blood samples were collected in plastic tubes containing a clot activator following overnight fasting. Samples were taken at hospital admission, before discharge, and at the one-month follow-up visit according to our institutional protocols and immediately delivered to our institutional laboratory.

Blood samples for NT-proBNP measurement were collected in EDTA-coated, aprotinin-containing test tubes, placed on ice (for up to 4 h), and centrifuged at 4500 rpm for 15 min at 0 ◦C. After centrifugation, the serum was extracted from the test tube and stored separately (at −80 ◦C). All NT-proBNP assays were done using a standard commercial kit (Roche Diagnostics, Rotkreuz, Switzerland) at a hospital's central independent laboratory.

Statistical Analysis

We reported continuous variables as mean ± SD or median and inter-quartiles range (IQR) as appropriate and categorical variables as absolute value and percentage. We used the Mann-Whitney test for continuous variables comparisons and the $\chi 2$ or the Fisher Exact test, as appropriate, for categorical variables.

To assess differences among NT-proBNP repeated measures (admission, discharge, and one-month follow-up), we evaluated NT-proBNP logarithmically transformed values by a two-way analysis of variance (ANOVA). Whenever ANOVA revealed a significant difference among baseline, discharge, and 1-month follow-up NT-proBNP measures, differences within groups were assessed "post-hoc" by the Newman-Keuls test.

The estimated treatment effect was reported as the ratio of the geometric means, based on the least squared means from an analysis of the covariance model (with logarithmic baseline value as a covariate) and the corresponding 2-sided 95% CI.

We performed the survival analysis with Kaplan-Meier curves and the log-rank test. We tested the associations between clinical variables and events using logistic regression analysis to adjust for covariates and time.

The power calculation for the study's primary endpoint is available as Supplementary material (table S2). Statistical significance was defined as $p<0.05$. PASS version 16 (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass), NCSS version 12 (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss), and MedCalc Statistical Software version 19.2.6 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org) were used for all the statistical analysis and graphical output.

Ethical issues

Our study is an observational retrospective analysis. However, as routine for our Institution, upon admission, each patient provided written informed consent to use for scientific purposes their clinical data in an anonymized fashion. The study protocol agreed with the ethical guidelines of the 1975 Declaration of Helsinki.

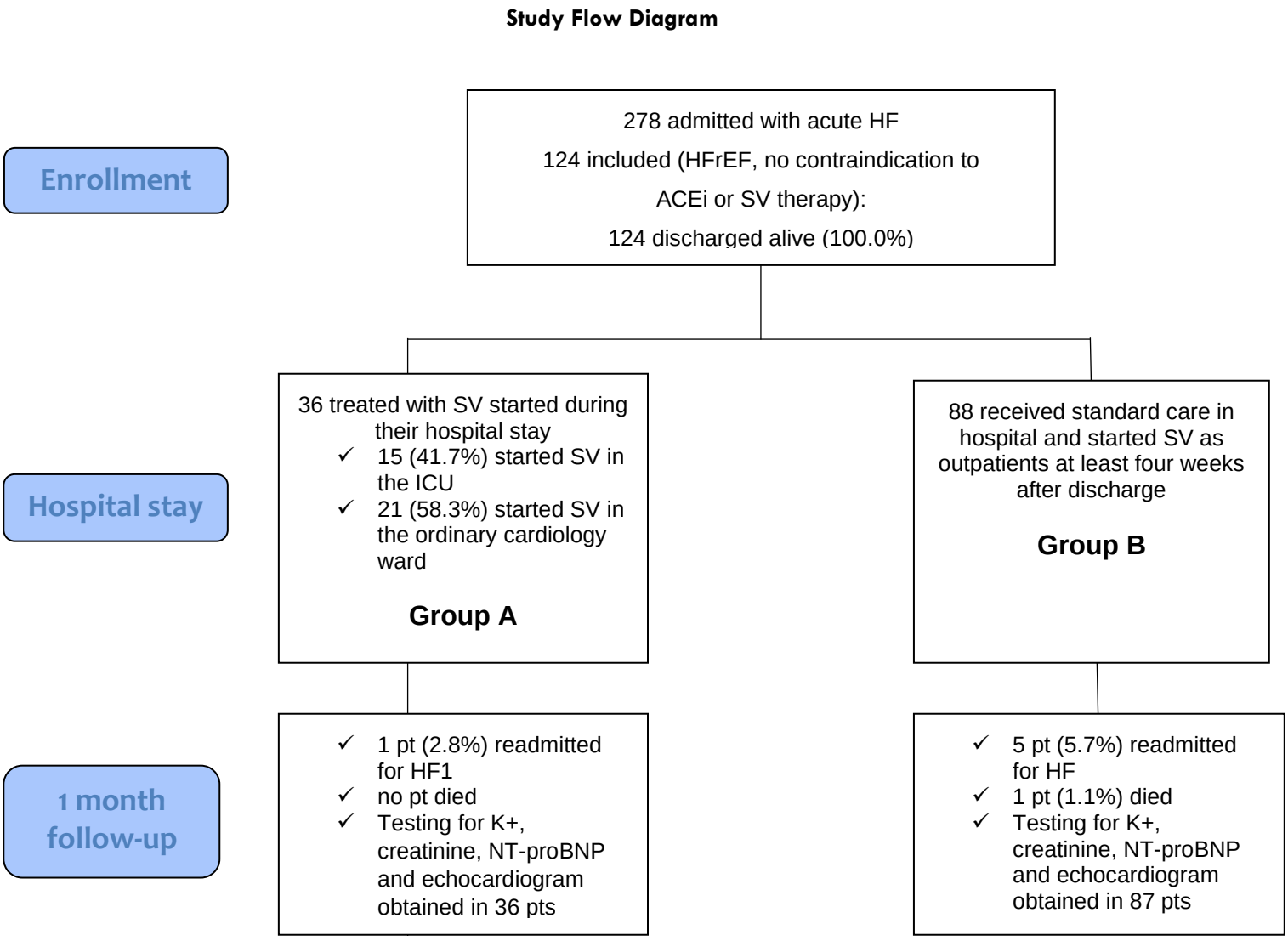
Results

Study population

The flow chart of the study is represented as a CONSORT diagram in figure 1. From January 1st to December 31st, 2018, 278 patients were admitted to the Cardiology Division of our Institution for acute HF. Of them, 124 patients fulfilled our study's inclusion and exclusion criteria and were included in our analysis. The clinical characteristics of the study population are summarised in table 1. In 36 patients, SV was started during their hospital stay (Group A). Of them, 15 (41.7%) started SV in the ICU at 2.1 ± 1.3 days from admission, and 21 (58.3%) started SV in the ordinary cardiology ward at 3.4 ± 1.5 days from admission. The remaining 88 patients received standard care during the hospital stay and were scheduled to start SV at least four weeks after discharge as outpatients (Group B).

Clinical characteristics of the study population at admission

Figure 1: CONSORT study flow diagram



(HF = heart failure, HFrEF = heart failure with reduced ejection fraction, ACEi = ACE inhibitors, SV = sacubitril/valsartan, ICU = intensive care unit)

Table 1: Clinical, laboratory, and instrumental characteristics of the study population

	Group A (36 pts)			Group B (88 pts)			
	Count	**Mean / %**	**SD / IQ**	**Count**	**Mean / %**	**SD / IQ**	**p level**
Age		73.8	11.3	88	76.4	11.4	0.25
Male sex	24	66.7%		49	55.7%		0.26
Ipertension	17	47.2%		60	67.8%		0.040
Diabetes	17	47.2%		18	20.7%		0.007
CKD (eGFR<60mL/min/1,73m2)	31	86.1%		40	45.5%		<0.0001
COPD	16	44.4%		25	28.7%		0.11
Previous CAD	24	66.7%		20	22.7%		<0.0001
Previous CHF	17	47.2%		16	18.2%		0.003
Previous NVAF	14	38.9%		30	34.1%		0.62

LBBB	14	38.9%		14	15.9%		0.015
CHF device							
AICD	18	50.0%		19	21.6%		0.004
CRT	10	27.8%		10	11.4%		0.054
Admission:							
NYHA class 4	7	19.4%		19	21.6%		0.97
Atrial Fibrillation	12	33.3%		49	55.7%		0.023
Systolic arterial pressure (mmHg)		118.0	20.8		132.9	22.9	0.0007
Heart rate (bpm)		83.7	27.1		95.5	26.5	0.030
LVEF (%)		28.1	5.8		31.4	7.8	0.01
Mitral regurgitation grade (1-4)		1.6	1.0		1.4	1.0	0.31
Tricuspid systolic gradient (mmHg)		47.3	9.2		50.2	10.1	0.13
Admission therapy:							
ACE-i/ARB	15	41.7%		70	58.6%		0.10
Loop Diuretics	25	69.4%		71	50.7%		0.060
Beta-blockers	25	69.4%		69	60.9%		0.38
MRA	20	55.6%		70	24.3%		0.002
Digoxin	4	11.1%		69	14.5%		0.62
Clinical presentation:							
Peripheral congestion	27	75.0%		62	70.5%		0.61
Pulmonary edema	3	8.3%		9	10.2%		0.74
Ipovolemic shock	0	0.0%		0	0.0%		na
Cardiogenic Shock	1	2.8%		0	0.0%		0.32
Infection/sepsis	7	19.4%		16	18.2%		0.87
Laboratory on admission:							
Anemia (Hb levels < 12.0g/dL)	8	22.2%		26	29.5%		0.40
Haemoglobin (g/dL)		13.3	2.0		13.2	2.1	0.73
Creatinine (mg/dL)		1.3	0.4		1.2	0.5	0.36
eGFR (cc/min/1.73m^2)		60.5	19.8		63.9	18.6	0.11
Serum K+ (mEq/L)		4.0	0.3		3.8	0.4	0.39

(CKD = chronic kidney disease, eGFR = calculated glomerular filtration rate, COPD = chronic obstructive pulmonary disease, CAD = coronary artery disease, CHF = congestive heart failure, NVAF = non-valvular atrial fibrillation, LBBB = left bundle branch block, AICD = automatic implantable cardiac defibrillator, CRT = cardiac resynchronization therapy, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction, ACE-i = ACE-inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist, Hb = hemoglobin).

Table 2: In-hospital treatments and outcomes

	Group A (36 pts)			**Group B (88 pts)**			
	Count	**Mean / %**	**SD / IQ**	**Count**	**Mean / %**	**SD / IQ**	**p level**
In hospital therapy:							
IV Loop diuretics	25	69.4%		68	77.3%		0.39
ACE-i/ARB (*)	21 (*)	58.3%		68	77.3%		0.050
IV nitrates	9	25.0%		31	35.2%		0,260
Beta-blockers	29	80.6%		76	86.4%		0.45

IV MRA	23	63.9%		61	69.3%		0.57
Digoxin	10	27,8%		33	37.5%		0.29
IV Amines	7	19.4%		8	9.1%		0.17
Levosimendan	13	36.1%		6	6.8%		0.001
ARNI	36	100.0%		0	0.0%		na
ARNI starting dose (mg/day)		78.8	47.4		0.0	0.0	na
ARNI mean dose at discharge (mg/day)		95.6	64.7		0.0	0.0	na
Discharge therapy:							
ARNI	36	100.0%		0	0.0%		na
ARNI discharge dose		95.6	64.7		0.0	0.0	na
Amiodarone	5	13.9%		14	15.9%		0.76
ACE-i/ARB	0	0.0%		68	77.3%		<0.0001
Beta-blocker	28	77.8%		75	85.2%		0.36
Loop diuretics	33	91.7%		79	89.8%		0.74
MRA	31	86.1%		71	80.7%		0.45
Digoxin	8	22.2%		22	25.0%		0.74
Hospital stay		10.8	6.5		7.6	5.4	0.012
AF at discharge	9	25.0%		38	43.2%		0.048
In-hospital death	0	0.0%		0	0.0%		na
In-hospital renal deterioration	6	16.7%		14	15.9%		0.92
In-hospital ARNI start	36	100.0%		0	0.0%		na

(ACE-i = ACE-inhibitor, ARB = angiotensin receptor blocker, IV = intravenous, MRA = mineralocorticoid receptor antagonist, ARNI = angiotensin receptor neprilysin inhibitor, AF = atrial fibrillation).

Table 3: Trends for clinical, laboratory, and instrumental parameters from admission to one-month follow up

	Group A (36 pts)			**Group B (88 pts)**			
	Count	**Mean / %**	**SD / IQ**	**Count**	**Mean / %**	**SD / IQ**	**p level**
NYHA class (I-IV)							
admission		3.1	0.5		3.1	0.6	0.62
NYHA IV at admission (%)	7	19.4%		19	21.6%		0.79
discharge		2.1	0.3		2.0	0.3	0.11
1-month FUP		1.9	0.5		2.0	0.6	0.26
LVEF (%)							
admission		28.1	5.8		31.4	7.8	0.01
discharge		31.3	6.1		35.0	8.3	0.007
1-month FUP		38.3	8.3		38.3	9.7	0.99
Mitral regurgitation grade (IV)							
admission		1.6	1.0		1.4	1.0	0.31
discharge		1.4	0.8		1.4	0.8	0.77
1-month FUP		1.4	0.7		1.3	0.7	0.93
sPAP (mmHg)							
admission		47.3	9.2		50.2	10.1	0.13
discharge		36.4	8.2		39.1	8.1	0.11

1-month FUP	34.6	9.0	32.7	8.2	0.30
NT-proBNP levels (pg/mL)					
admission	7663.5	4073.8 - 12541.8	7528.0	4516.0 - 15598.5	0.44
discharge	2496.0	1480.0 - 3810.0	4632.5	2707.8 - 9921.3	<0.0001
1-month FUP	1653.0	881.3 - 2558.3	2599.0	1168.0 - 4557.0	0.27
Heart rate (bpm)					
admission	83.7	27.1	95.5	26.5	0.030
discharge	71.7	15.7	77.2	16.0	0.08
1-month FUP	70.8	12.4	77.1	15.7	0.022
Systolic arterial pressure (mmHg)					
admission	118.0	20.8	132.9	22.9	0.0007
discharge	112.4	18.2	122.5	16.5	0.005
1-month FUP	114.9	16.6	125.6	16.5	0.002
Serum creatinine levels (mg/dL)					
admission	1.3	0.4	1.2	0.5	0.36
discharge	1.3	0.4	1.3	0.4	0.50
1-month FUP	1.4	0.6	1.4	0.6	0.91
Serum K+ levels (mEq/L)					
admission	4.0	0.3	3.8	0.4	0.039
discharge	4.3	0.3	4.2	0.4	0.022
1-month FUP	4.8	0.5	4.5	0.5	0.011

(NYHA = New York Heart Association, FUP = follow-up).

The clinical characteristics of the 2 study groups at admission are summarised in table 1. Group A and B patient ages were similar (73.8 ± 11.3 vs. 76.4 ± 11.4 years, p=0.25), with no significant difference in male sex prevalence (66.7 and 57.5%, p=0.27).

In Group A, diabetes (47.2 vs. 20.7%, p=0.007), impaired renal function (86.1 vs. 45.5%, p<0.001), and coronary artery disease (66.7 vs. 22.7% p<0.001) were more common than in Group B. Conversely, systemic arterial hypertension was more prevalent in Group B than in Group A (67.8 vs. 47.2%, p=0.040).

Group A patients reported a 47.2% previous hospital admission rate for HF, a percentage significantly higher than in Group B (18.2%, p=0.003). The rates of HF clinical presentation with pulmonary congestion, pulmonary edema, peripheral congestion, and systemic hypoperfusion or cardiogenic shock were similar in the two groups, as well as the rate of NYHA class 4 at admission (19.4% in Group A and 21.6% in Group B, p=0.79) and the NT-proBNP levels (7663.5, IQR 4073.8-12541.8 pg/mL in Group A and 7528.0, IQR 4516.0-15598.5 pg/mL in Group B, p=0.37). In Group A, the mean systolic arterial pressure (118.0 ± 20.8 vs. 132.8 ± 22.9 mmHg, p<0.001) and the left ventricular ejection fraction (28.5±5.5 vs. 32.1±7.6, p=004) were significantly lower than in Group B. Atrial fibrillation was more common in Group B (55.7% vs. 33.3%, p=0.023), resulting into a slightly higher admission mean heart rate (95.5±26.5 vs. 83.7±27.1, p=0.030). The mitral regurgitation grade and the systolic tricuspid gradient were similar in the two groups.

The two patient groups were on similar medical therapies, except for a higher treatment rate with mineralocorticoid receptor antagonists in group A (55.6% vs. 24.3%, p=0.002) which resulted in slightly higher potassium levels (4.0±0.3 vs. 3.8±0.4 mEq/L, p=0.039).

In-hospital treatment and in-hospital outcomes

In-hospital treatment and outcomes are summarised in Tables 2 and 3. No patient died during the hospital stay, which was longer in Group A (10.8±6.5 vs. 7.6±5.4 days, p=0.012). Sacubitril/valsartan was started in all Group A patients during the hospital stay, as for definition, with mean starting and discharge doses of

77.8±47.4 and 96.5±64.5 mg/day, respectively. The remaining HF therapies of the two groups were similar, except for the more frequent use of intravenous levosimendan in Group A (36.1 vs. 6.8%, p=0.001).

At discharge, NYHA class was improved to similar grades in the two groups (2.1±0.3 and 2.1±0.3, p=0.11). LVEF also improved in both groups but remained significantly lower in Group A (31.3±6.1 vs. 35.0±8.3, p=0.007), while NT-proBNP levels improved in both groups but much more in Group A, resulting in lower predischarge values (2496.0, 1480.0 to 3810.0 vs. 4558.0, 2041.5 to 9733.8 pg/mL, p<0.032) (figure 2). The time-averaged mean NT-proBNP reduction was significantly higher in group A patients (-0.30, 95% CI -0.40 to -0.21, <0.0001 vs. group B, figure 3). Mean systolic blood pressure remained slightly lower in Group A (112.4±18.2 vs. 122.5±16.5, p<0.005), but no severe hypotension was observed in the two groups. The rate of renal function deterioration during the hospital stay (16.7% vs. 15.9%, p=0.92) and discharge creatinine levels (1.3±0.4 vs. 1.3±0.4 mg/dL, p=0.99) were also similar between the two groups. Discharge potassium levels were slightly higher in Group A (4.3±0.3 vs. 4.2±0.4, p=0.022), but no severe hyperkaliemia was observed in the study population during the hospital stay.

Multivariate analysis suggested diabetes, coronary artery disease, higher systolic blood pressure, and the need for inotropic support as independent predictors for in-hospital SV treatment (table 4).

Table 4: independent predictors for starting ARNI before discharge according to logistic regression analysis

Independent variable: ARNI start before discharge

	Univariate Analysis				Multivariate Analysis		
Dependent Variables	**Odds ratio**	**95% CI**	**P**	**Variable**	**Odds ratio**	**95% CI**	**P**
Hypertension	0.31	0.09 - 1.06	0.06	**Hypertension**	0.44	0.15 - 1.27	0.13
Diabetes	6.37	1.69 - 24.08	0.006	**Diabetes**	3.86	1.28 - 11.61	0.016
Previous MI or revascularization	4.73	1.42 - 15.78	0.012	**Previous MI and/or revascularization**	5.07	1.85 - 13.92	0.002
Previous admission for heart failure	2.29	0.64 - 8.12	0.20	-			
Atrial fibrillation (history or current)	2.06	0.60 - 7.21	0.26	-			
Admission SAP (for mmHg)	0.97	0.95 - 1.02	0.07	**Admission SAP (for mmHg)**	0.97	0.95 - 0.99	0.02
Admission LVEF (for % value)	0.95	0.88 - 1.02	0.13	-			
Admission NT-proBNP (for pg/mL)	1.00	0.99 - 1.00	0.20	-			
Admission creatinine (for mg/dL)	0.64	0.13 - 3.17	0.57	-			
Need for inotropic support	5.07	1.08 - 23.86	0.04	**Need for inotropic support**	5.70	1.59 - 20.37	0.007
Need for IV vasodilators	0.65	0.17 - 2.39	0.52	-			
Age (for 1 year)	1.01	0.95 - 1.08	0.77	-			
Male sex	0.77	0.22 - 2.70	0.69	-			
Peripheral congestion	0.92	0.28 - 3.03	0.89	-			

Final Model Goodness of Fit Test

Null model -2 Log Likelihood	148.716
Full model -2 Log Likelihood	101.131
Chi-square	47.585
DF	5

Significance level	P < 0.0001

Hosmer & Lemeshow test	
Chi-square	8.3339
DF	8
Significance level	P = 0.40

(ARNI = angiotensin receptor neprilysin inhibitor, CI = confidence interval, MI = myocardial infarction, SAP = systolic pulmonary pressure, LVEF =left ventricular ejection fraction, IV = intravenous).

Figure 2: Logit NT-proBNP levels at admission, discharge, and one-month follow-up) in patients treated with ARNI in the hospital (Group A) vs. patients scheduled to start ARNI at the one-month follow-up visit (Group B).

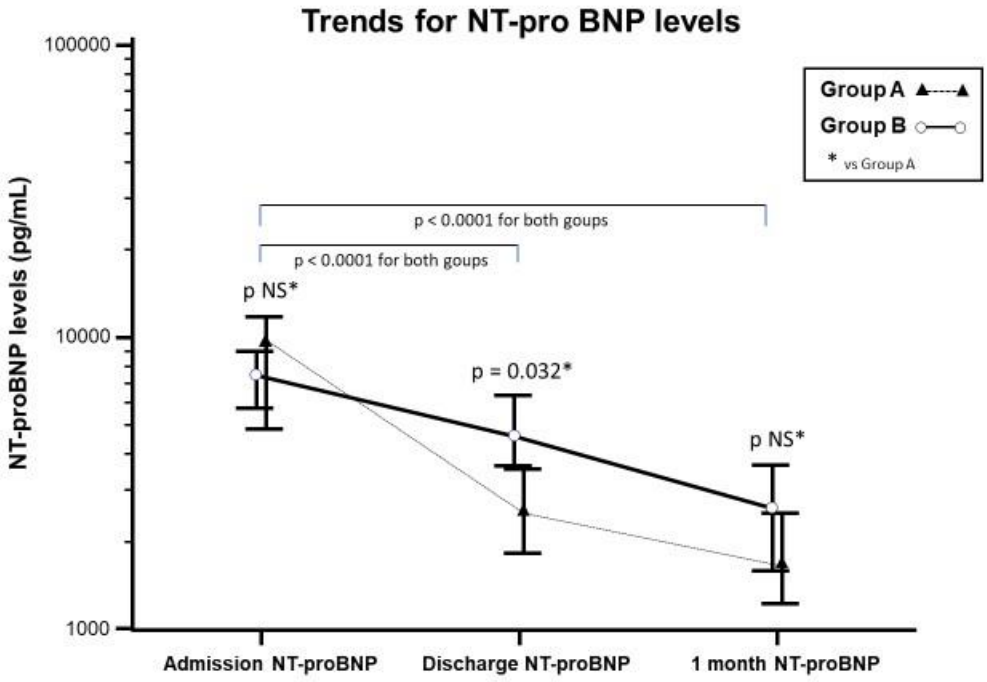
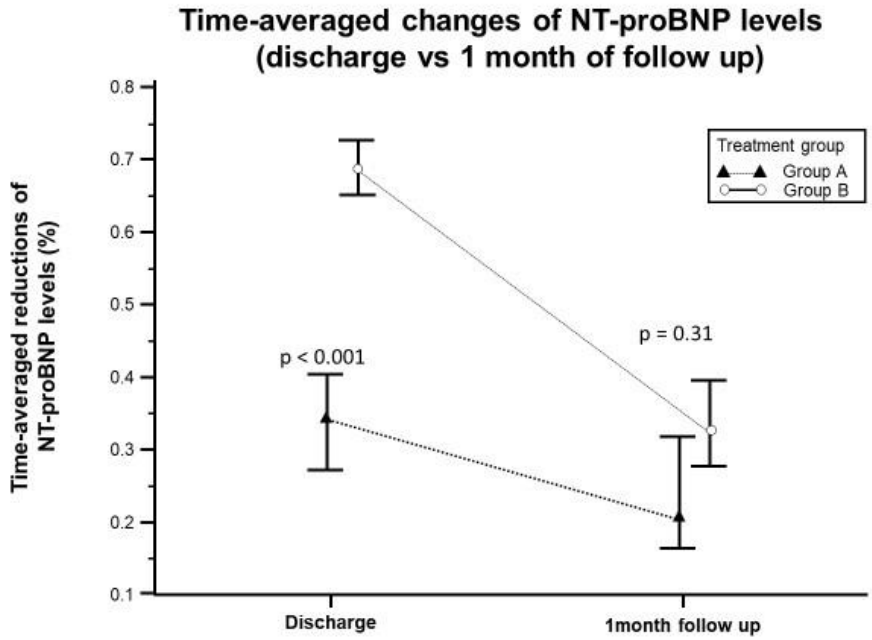


Figure 3: Time-averaged changes of NT-proBNP levels (discharge vs. one-month follow-up) in patients treated with ARNI in the hospital (Group A) vs. patients scheduled to start ARNI at the one-month follow-up visit (Group B).



One-month follow-up

One-month follow-up outcomes are summarized in table 5. Within the first month from discharge, only one Group B patient had died (1.1%), while one patient in Group A (2.8%) and five in Group B (5.7%, p=0.43, figure S1) had been readmitted to the hospital for CHF. In Group A, the persistence in SV therapy was 97.4%, with a mean dose of 127.9±82.7mg/day.

At the 1-month follow-up visit, NYHA class was similar in the two groups (1.9±0.5 vs. 2.0±0.6. p=0.26). NT-proBNP further lowered in both groups, leveling to similar levels (1653.0, IQ 881.3-2558.3 vs. 2599.0, IQ 1168.0-4557.0 pg/mL, p =0.27). LVEF also recovered in both groups leading to similar 1-mont measures (38.3±8.3 vs. 38.3±9.7, p=0.98). In Group A, systolic arterial pressure remained slightly lower (114.9±16.6 vs. 125.6±16.5, p=0.002), and serum K+ levels slightly higher (4.8±0.5 vs. 4.5±0.5, p=0.011). Serum creatinine levels at 1-month follow-up were similar in the two groups (1.4±0.6 vs. 1.4±0.6 mg/dL. p=0.91).

Table 5: Clinical outcomes at the one-month follow-up.

	Group A (36 pts)			Group B (88 pts)			
	Count	**Mean / %**	**SD / IQ**	**Count**	**Mean / %**	**SD / IQ**	**p level**
1-month outcomes:							
ARNI persistence	33	97.4%		0	0.0%		na
ARNI dose		127.9	82.7	0	0.0%		na
rehospitalization for HF	1	2.8%		5	5.7%		0.43
all-cause death	0	0.0%		1	1.1%		0.32
cardiac death	0	0.0%		1	1.1%		0.53

(SD = standard deviation, IQ = interquartile range, ARNI = angiotensin receptor neprilysin inhibitor, HF = heart failure).

Discussion

The present study demonstrated that in the real-world population evaluated, the SV treatment started in-hospital in patients with acute HFrEF was associated with a faster NT-proBNP recovery compared to patients scheduled for starting SV four weeks after discharge according to PARAGON-HF study protocol[1] and current HF ESC guidelines[18]. This result was accomplished without excess adverse effects, as early SV treatment did not increase the occurrence of severe hypotension, hyperkalemia, and renal function impairment compared to patients with standard treatment.

In our study, patients treated with SV during their hospital stay showed a much higher risk profile than patients with standard treatment, showing more than double diabetes, more than triple coronary artery disease, and a fivefold need for levosimendan infusion rates, and with significantly lower systolic blood pressure and LVEF on admission. Nevertheless, the time-averaged mean NT-proBNP reduction, the primary endpoint of the present study, was significantly more pronounced in patients treated early with SV at discharge. These findings paralleled the results of the pivotal RCT PIONEER-HF[8], which first reported that the in-hospital initiation of SV therapy led to a more significant reduction in the NT-proBNP concentration than standard enalapril therapy. Similar results were reported in the TRANSITION trial[7, 19, 20], which reported in patients with HFrEF starting SV in-hospital a rapid reduction in NT-proBNP, statistically significant at discharge. Similar to our report, NT-proBNP levels trended to similar results four weeks after discharge in both groups, regardless of the timing of SV treatment [20]. The favorable biomarker response over time of early SV treatment seems relevant from a clinical point of view, as it was associated with a better clinical prognosis in both PIONEER-HF and TRANSITION post-hoc analyses. Our study confirmed the biomarker effects of starting ARNI as soon as possible during the hospital stay, but the population studied was too small to detect any significant difference in hard endpoints.

Even if a few papers claimed that PIONEER-HF and TRANSITION populations were somewhat representative of the real-world [21], many others found that only a minority of real-world patients fulfill the inclusion and exclusion criteria of the pivotal studies [22-25]. Our study presented data from real-world patients with a much higher risk profile than those enrolled in the RCTs, in line with other reports [26, 27]. First, the mean age of our study population was much higher than that reported by PARADIGM-HF[1], PIONEER-HF[8], and TRANSITION[7] RCTs. Second, on admission, we enrolled patients with higher NYHA III/IV rates and very high NT-proBNP levels compared to RTCs[1, 7, 8]. Other real-world studies reported values of NT-proBNP on admission similar to our study, also in patients selected according to PIONEER-HF protocol inclusion and exclusion criteria[25]. Third, the prevalence of implanted devices (CRT-P, CRT-D, and CCM) in our study was much higher than that reported by RCTs[1, 7, 8]. Fourth, many patients in our study needed in-hospital intravenous inotropic drug treatment (generally levosimendan). Only a few reports evaluated the effects of ARNI administered in advanced decompensated HF [10], and no data are available from the pivotal RCTs publications in this particular clinical subset. Finally, many patients in our study started ARNI in the ICU, often naïve from ACE inhibitors of AT2-antagonists. Even in this case, only a few studies reported the outcomes of early ARNI administration in patients with acute HF [10, 11], and the RCTs offer no additional information.

Our observational study offers some insights into the reasons which prompted clinicians to anticipate ARNI treatment during hospitalization. We built a multivariate model indicating that diabetes, coronary artery disease, higher systolic blood pressure, and the need for inotropic support were independent predictors for in-hospital ARNI treatment. Many considerations could favor the decision to start ARNI before discharge[28], ranging from an expected better therapeutic adherence to the need to cover the most critical phase for patients recovering from HF decompensation. Our experience indicates that clinicians tried to balance a more aggressive approach to higher-risk HFrEF patients with the need to avoid hypotension, the nastiest side effect in treating patients with acutely decompensated HF.

Despite the high-risk features of our real-world HFrEF population, early ARNI therapy was safe, with only a modest reduction of blood pressure levels, a few patients with worsening pre-existing renal impairment, and no case of severe hyperkalemia. These observations confirmed the excellent safety profile reported in RCTs[1, 7, 8].

Other few studies reported about starting ARNI early, during the hospital stay of patients admitted for HFrEF. Liang et al. [9] compared acutely decompensated HFrEF patients treated during their hospital stay with SV with propensity score-matched controls. The study showed better clinical outcomes in patients treated with SV but did not report changes in NT-proBNP or other biomarkers in response di SV therapy. Chng et al. [12] reported

a retrospective comparison of patients with HFrEF starting ARNI in the hospital or after discharge, showing higher rates of drug-related adverse events and ARNI discontinuation in inpatients. Again the study did not report data about natriuretic peptide changes in response to ARNI treatment. Akerman[13], Peppin[14], and Acanfora[15] reported case series of patients hospitalized for acute HFrEF treated with SV before discharge, with NT-proBNP level reductions and safety issues comparable to our study.

The advantages of starting early SV during hospitalizations for acute HFrEF parallel those observed for other novel heart failure treatments. In particular, SGLT2 inhibitors, which have been shown to dramatically improve prognosis when added on top of treatment in stable patients with heart failure, have been tested early treatment during the acute phase of hospitalization for HFrEF[29]

In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial, patients with HF and diabetes were randomized to sotagliflozin or placebo before or shortly after discharge following hospitalization for acute heart failure[30]. In this study, sotagliflozin reduced the primary endpoint compared to the placebo and documented a 29% reduction in the first occurrence of cardiovascular death or HF hospitalization. More recently, early treatment with empagliflozin in patients hospitalized for acute HF was evaluated in the EMPULSE trial [31, 32]. Empagliflozin reduced the primary composite endpoint of death, number of HF events, time to first HF event, and change from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) at 90 days of treatment. The clinical benefit rates were 53.9% in the empagliflozin-treated patients and 39.7% in the placebo group (p = 0.0054). This evidence earned a class I/C recommendation in the ESC 2021 Guidelines[6] for using novel evidence-based oral medical treatments before discharge in patients hospitalized for acute heart failure.

Limitations

The observational design of our study suffers from the limitations typical for non-randomized studies. The differences in NT-proBNP levels, mortality, hospital readmissions for CHF, and other endpoints may be affected by selection bias, even after careful adjustment for demographic and clinical confounders. Thus, our results should be considered confirmatory, hypothesis-generating, or both. However, external validation in observational studies is increasingly considered essential to generalize the results of randomized trials, potentially hampered by strict inclusion and exclusion criteria[33].

Second, the patient population evaluated was small, enough to assess changes in NT-proBNP levels during the hospital stay and short-term follow-up but insufficient to assess clinically meaningful differences in hard endpoints. Nevertheless, the present study's sample size guaranteed the primary endpoint enough statistical power to reject the null hypothesis (table S2).

Third, our study enrolled a single-center patient cohort with a potential bias regarding ethnicity, environment, and local clinical practices. Thus, caution should be taken before extrapolating the results of our study to the general population.

Fourth, patients starting SV in the hospital were treated more frequently with levosimendan and other inotropic drugs. It might be argued that inotropic treatment "per se" could have favored NT-proBNP levels recovery, but the trend for more rapid natriuretic peptides level improvement remained substantially unchanged when patients treated with levosimendan were excluded from the analysis (figure S2).

Finally, we limited our analysis to patients hospitalized before 2019 to avoid the confounding factor of SARS-CoV2-related heart diseases[34].

Conclusions

Our study confirmed in a high-risk real-world HFrEF population that starting ARNI as soon as possible before discharge is associated with faster NT-proBNP levels recovery. More extensive prospective studies are warranted to assess if a more rapid NT-proBNP level improvement might translate into significant clinical benefits.

Conflict of interest

Dr. Alessandro Lupi received speaker honoraria from the drug company Novartis. Prof. Roberto De Ponti received honoraria from Biosense-Webster and Medtronic for lectures and scientific collaborations. All other authors declare no conflict of interest.

Acknowledgments

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Supplementary Material

Figure S1 - Survival free from rehospitalization for heart failure according to Kaplan Mayer curves and log-rank test results in patients treated with ARNI in hospital (Group A) vs. patients scheduled to start ARNI at the one-month follow-up visit (Group B).

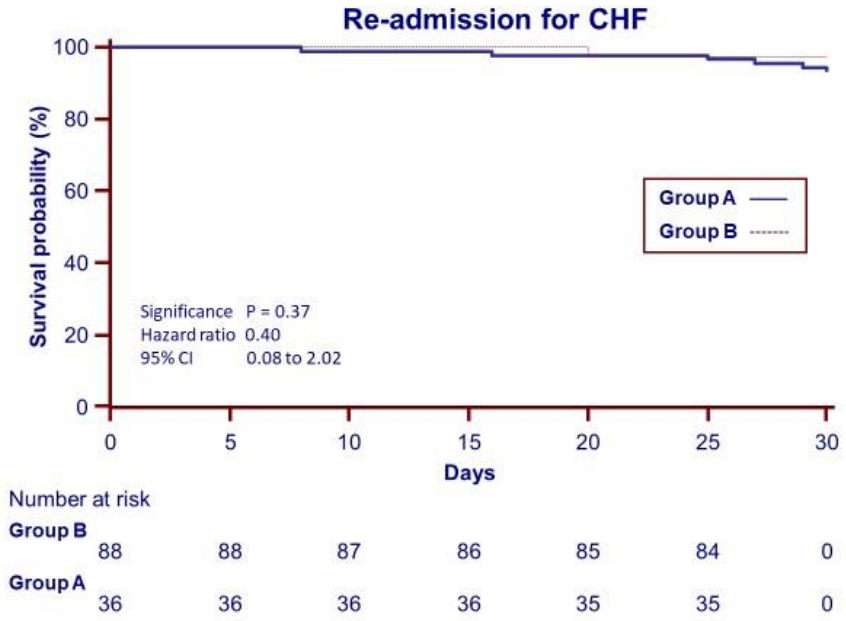
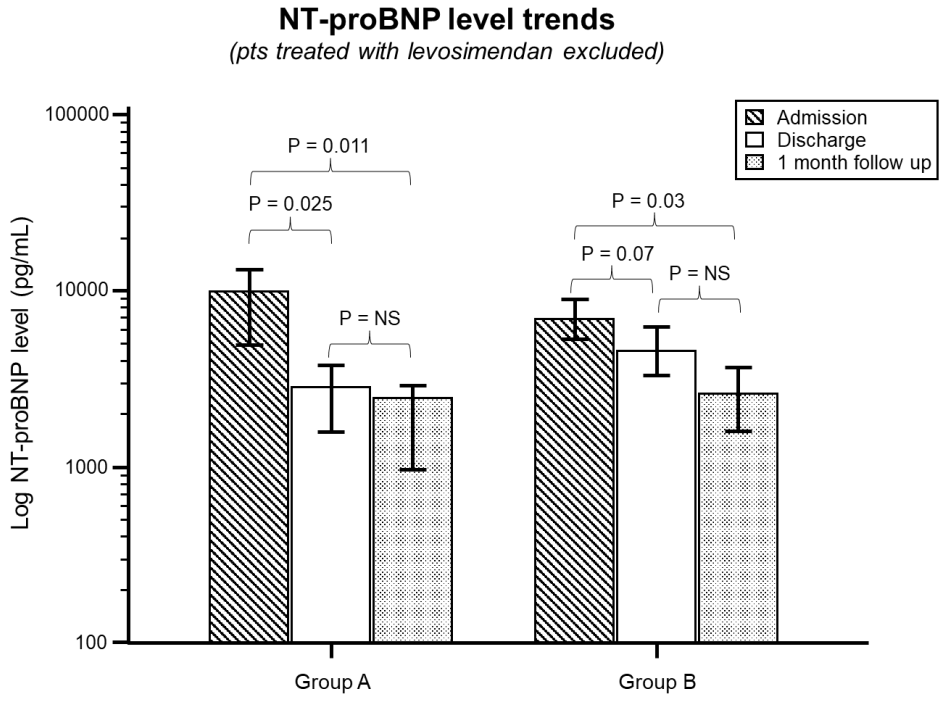


Figure S2 - Sensitivity analysis excluding patients treated with levosimendan. Logit NT-proBNP levels at admission, discharge, and one-month follow-up) in patients treated with ARNI in the hospital (Group A) vs. patients scheduled to start ARNI at the one-month follow-up visit (Group B).



Supplementary Table 1 – Statistical power calculation for the study's primary endpoint (difference in time-averaged mean NT-proBNP reduction from admission to discharge in patients treated with ARNI during the hospital stay, Group A, and scheduled patients for starting ARNI four weeks after discharge, Group B).

Tests for Two Proportions in a Repeated Measures Design

Numeric Results
Test Statistic Based on Difference: P1 - P2.
One-Sided Test. Null Hypothesis: OR = 1. Alternative Hypothesis: OR > 1 (or OR < 1).
Covariance Type = Compound Symmetry

Power	N1	N2	N	M	P1	P2	OR1	Rho	Alpha
0.99438	36	88	124	2	0.342	0.684	0.240	0.500	0.050

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Report Definitions
Power is the probability of rejecting a false null hypothesis.
N1 and N2 are the numbers of items sampled from each population.
N is the total sample size, N1 + N2.
M is the number of time points (repeated measurements) at which each subject is observed.
P1 and P2 are the proportions from groups 1 and 2, respectively.
OR1 is the odds ratio ((P1/(1-P1))/(P2/(1-P2))) to be detected.
Rho is the correlation between observations on the same subject.
Alpha is the probability of rejecting a true null hypothesis.

Summary Statements
Group sample sizes of 36 and 88 achieve 99.438% power to detect an odds ratio of 0.240 in a design with 2 repeated measurements having a Compound Symmetry covariance structure when the proportion from group 2 is 0,684, the correlation between observations on the same subject is 0,500, and the alpha level is 0,050.