

# Impacto da Suplementação de Vitamina D numa População com Insuficiência Cardíaca

## *Impact of Vitamin D Supplementation in a Heart Failure Population*

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### Resumo:

**Introdução:** O défice de vitamina D (VD) é uma comorbilidade associada frequentemente à insuficiência cardíaca (IC). Os efeitos da suplementação da VD nestes doentes são desconhecidos. Este estudo pretende avaliar o impacto da correção do défice de VD em doentes com IC.

**Material e Métodos:** Neste estudo de centro único, observacional retrospectivo, foram incluídos doentes com défice de VD admitidos numa clínica de IC. A VD foi prescrita com reavaliação sérica aos 12 meses. A amostra foi dividida em 2 grupos: [VD (+): défice VD corrigido] e [VD (-): défice VD mantido]. As variáveis foram analisadas em ambos os grupos.

**Resultados e Conclusão:** Foram incluídos oitenta e sete doentes, sem diferenças estatisticamente significativas nas características basais entre os dois grupos. Foi reportada baixa adesão terapêutica em 40% do grupo VD (-). Após tratamento com VD, não se verificaram diferenças estatisticamente significativas entre os dois grupos na classe de NYHA I, NT-proBNP, hospitalizações por IC no ano anterior, pontuação no *Duke Activity Score Index* e na distância do teste de 6-minutos de marcha. No grupo VD (+) verificou-se um decréscimo estatisticamente significativo dos valores séricos do NT-proBNP ao longo do tempo ( $1740 \pm 2761$  pg/mL para  $851 \pm 1436$  pg/mL,  $p = 0,001$ ). Verificou-se, em ambos os grupos, uma redução nas hospitalizações por IC no ano anterior comparando o basal com avaliação aos 12 meses ( $1,02 \pm 0,67$  para  $0,29 \pm 0,82$ ,  $p < 0,001$  e  $1,03 \pm 1,04$  para  $0,40 \pm 0,81$ ,  $p = 0,001$ , para o grupo VD (+) e VD (-), respetivamente). A correção do défice da VD não influenciou as variáveis analisadas. As melhorias observadas nos grupos poderão refletir o impacto da abordagem multidisciplinar pela clínica de IC.

**Palavras-chave:** Deficiência Vitamina D; Insuficiência Cardíaca; Vitamina D.

### Abstract:

**Introduction:** Vitamin D (VD) deficiency is a major comorbidity, frequently associated to heart failure (HF). VD supplementation effects in these patients remain unknown. Therefore, this study aims to evaluate the impact of VD deficiency treatment or therapy correction in HF patients' cohort.

**Material and Methods:** Observational retrospective single-center study enrolling patients admitted to a HF clinic with VD deficiency. VD was prescribed to these patients with reassessment of its levels 12 months later. Study population was divided in: [VD (+) group: corrected VD deficiency] and [VD (-): maintained VD deficiency]. Variables were analysed in both groups.

**Results and Conclusion:** Eighty-seven patients were included with no difference of baseline characteristics between the groups. Poor compliance was reported in 40% of VD (-) patients. After treatment, there were no statistically difference in variables analysed between the two groups: NYHA class I, NT-proBNP, HF hospitalizations in the previous year, Duke Activity Score Index score and 6 minute Walking Distance. VD (+) group had a statistically significant decrease of NT-proBNP level over time ( $1740 \pm 2761$  pg/mL to  $851 \pm 1436$  pg/mL,  $p = 0.001$ ). Statistically, both groups had a significant reduction of the number of HF hospitalizations, between baseline and 12 months later ( $1.02 \pm 0.67$  to  $0.29 \pm 0.82$ ,  $p < 0.001$  and  $1.03 \pm 1.04$  to  $0.40 \pm 0.81$ ,  $p = 0.001$ , for VD (+) and VD (-), respectively). Therefore, the correction of VD deficiency did not have impact in the variables analysed. The improvements reported within both groups may reflect the impact of the HF clinic optimized care.

**Keywords:** Heart Failure; Vitamin D; Vitamin D Deficiency.

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### Introduction

Vitamin D (VD) deficiency is a major health problem, present in around 30%-50% of world population.<sup>1</sup> Heart failure (HF) remains a relevant public health disease due to its high prevalence and its major impact on elderly population hospitalizations.<sup>2</sup> There is a frequent association between VD

deficiency and HF disease, related in 80% to 95% of the cases.<sup>3</sup> VD deficiency has been strongly associated to an increased risk of developing HF, also to worst HF-related outcomes and higher risk of HF hospitalization (hHF) consequently to death in these patients.<sup>1,2,4-6</sup> It has also been correlated with greater incidence of depression and cognitive dysfunction in HF population.<sup>5,7</sup>

VD is associated to specific anti-inflammatory effects by suppressing the release of inflammatory factors like tumor necrosis factor and increasing serum concentrations of anti-inflammatory cytokines such as interleukin 10 in HF patients. Nevertheless, trials of VD supplementation have shown inconclusive results and this practice is not currently recommended, neither to reduce the risk of heart failure, nor to improve HF-related outcomes.<sup>1,3,6,8-10</sup> However, the myocardium is considered to be an important target of 25 (OH)D and 1.25 (OH)<sub>2</sub>D and VD status could influence left ventricle LV structure and function.<sup>11,12</sup>

These inconclusive data encouraged us to conduct a study on the impact of vitamin D supplementation in heart failure patients with VD deficiency.

The present study aims to evaluate clinical, analytical and functional impact of the VD deficiency in a cohort of HF patients followed-up in a heart failure clinic

## Methods

In this observational retrospective single-center study, we included all patients admitted to our HF clinic from January 2015 to December 2018 with VD deficiency (< 50 nmol/L) at admission. Patients with stage 5 of chronic kidney disease by the National Kidney Foundation (NKF) classification, those with incomplete follow-up and those who were previously under VD treatment were excluded.

All patients were enrolled in an outpatient setting and received a prescription of oral cholecalciferol. Data concerning dosage or adherence to treatment were retrieved from electronic medical records. Serum VD (25-OH-vitamin D) level was checked after one-year supplementation and study population was grouped within two groups: VD deficiency corrected [VD (+) group] and VD deficiency maintained [VD (-) group]. A descriptive analysis was carried out to characterize baseline profile of each group. Functional variables and vital outcomes were compared in both groups, before and after cholecalciferol therapy, in order to evaluate the impact of VD deficiency correction: New York Heart Association (NYHA) functional class as a subjective scale of symptoms; N-terminal-pro hormone B-type natriuretic peptide (NT-pro-BNP) as a prognostic serum biomarker; Duke Activity Status Index (DASI) as a self-administered questionnaire that assesses the functional capacity of patients with cardiovascular disease, and Six-Minute Walk Test Distance (6MWD) as an objective measure of functional capacity. We also evaluated hHF and mortality during one year after treatment.

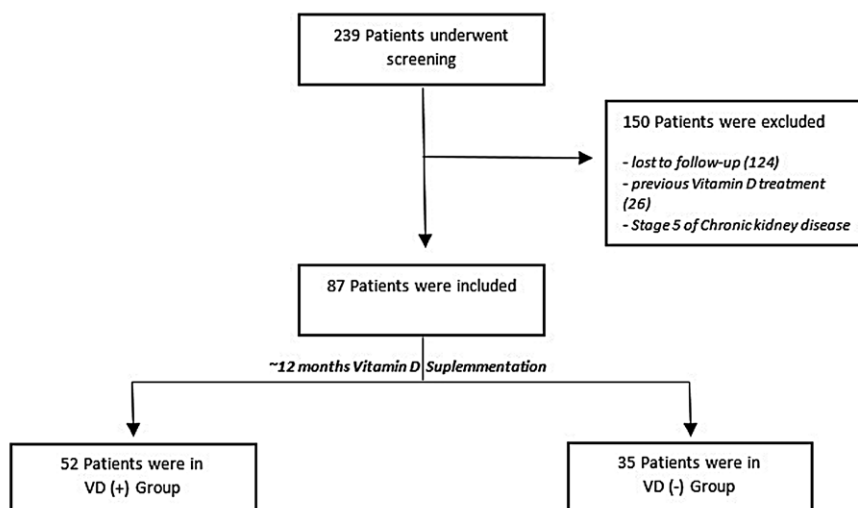
All data were collected from electronic medical records. Descriptive and statistical analysis was performed using IBM SPSS Statistics, version 27.0, IBM Corp, Armonk, NY. Categorical variables are presented as number of cases and percentage. Continuous variables are presented as mean and standard deviation from the mean or median and interquartile ranges as appropriate. One-sample Kolmogorov-Smirnov test, Shapiro-Wilk test, analysis of kurtosis, skewness and normal Q-Q plots were used to assess normality of distribution within groups of study. Categorical variables were compared using Fisher's exact test or chi-square test, as appropriate. For continuous variables, we used Mann-Whitney U or t-test for independent samples to compare the initial characteristics between the two groups, and a repeated measures analysis (ANOVA), Wilcoxon signed ranks test or paired t-test as appropriate to compare the evolution of continuous variables within and between groups. All reported p-values are two-tailed and statistical significance was considered if p values were <0.05.

## Results

From a total of 239 patients admitted to our HF clinic from January 2015 to December 2018 with VD deficiency, 152 were mostly excluded due to incomplete follow-up (discharge of HF clinic or absence of reevaluation of VD level at 12 months) as shown in Fig. 1. The remaining 87 patients defined the study population. After approximately one-year of oral VD supplementation there were 52 (60%) patients with normal VD level [VD (+) group] and 35 (40%) patients that maintained VD deficiency [VD (-) group]. The baseline characteristics of both groups are depicted in Table 1 and were not statistically different regarding all the variables analysed. This was predominantly an elderly and female population, with a mean age of 74 years-old and with high prevalence of comorbidities such hypertension, diabetes *mellitus* and atrial fibrillation. In the VD (+) group, the major HF etiology was non-ischemic with reduced (< 40%) left ventricle ejection fraction (LVEF) and in VD (-) group was predominantly ischemic with non-reduced LVEF. Regarding HF medications, in the VD (+) group and VD (-) group respectively, 65% and 67% of patients with reduced LVEF were taking angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin II receptor neprilysin inhibitor and 88% and 72% were taking beta-blockers.

As shown in Table 2, the supplementation period (median of 12 months) as well as VD monthly intake were similar in both groups (median of 22 400 International Units). According to clinical records, VD (-) group had poor compliance. Exclusion of the non-compliant patients of VD (-) group did not alter the following results (data not shown).

Comparison of clinical variables between the two study groups before and after VD supplementation are exhibited in Table 3. Before VD supplementation, both groups were similar in terms of NYHA class, NT-proBNP, DASI and 6MWD. There


**Figure 1:** Study enrollment and follow-up.

VD (+) group: patients whose vitamin D deficiency has been corrected; VD (-) group: patients whose vitamin D deficiency maintained after supplementation

**Table 1:** Baseline characteristics of study population

Variable	Baseline		
	VD (+)*	VD (-)*	p value †
	n (%) = 52 (60)	n (%) = 35 (40)	
Male, n (%)	24 (46)	15 (43)	0.467
Age in years, mean (SD)	73 (12)	75 (10)	0.513
Hypertension, n (%)	45 (87)	31 (89)	0.526
Diabetes mellitus, n (%)	30 (58)	21 (60)	0.504
Obesity, n (%)	16 (31)	13 (37)	0.348
Atrial Fibrillation, n (%)	30 (58)	19 (54)	0.462
LVEF <40%, n (%)	32 (64)	18 (36)	0.237
Etiology of HF, n (%)			
Ischemic	20 (39)	21 (60)	0.053
Non-Ischemic	32 (61)	14 (40)	
Drugs in HFrEF patients, n (%)	32 (100)	18 (100)	
ACEI/ARB	19 (59)	10 (56)	0.512
ARNI	2 (6)	2 (11)	0.456
BB	28 (88)	13 (72)	0.167
MRA	16 (50)	7 (39)	0.323
IV	1 (3)	2 (11)	0.291
DIG	6 (19)	3 (17)	0.587

ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor blockers; ARNI, angiotensin II receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; HF, heart failure; HFrEF, heart failure reduced left ventricular ejection fraction; IV, ivabradine; LVEF, left ventricular ejection fraction; MRI, aldosterone receptor antagonists; NYHA, New York Heart Association; SD, standard-deviation.

\* VD (+) refers to the group that corrected vitamin D deficiency; VD (-) refers to the group that persisted with VD deficiency.

† Chi-square, Fisher's exact test or t-test for independent samples, as appropriate.

was also no difference in number of hHF in the 12-month period before enrollment.

There was a higher number of patients in NYHA class I after 12-month follow-up in both groups, but the difference between groups was not statistically significant ( $p = 0.291$ ) - Table 3.

As seen in Fig. 2, after one-year of VD supplementation,

both groups showed a decrease in median levels of NT-proB-NP with VD treatment; (VD (+) group:  $1740 \pm 2761$  pg/mL to  $851 \pm 1436$  pg/mL,  $p = 0.001$  vs VD (-) group:  $902 \pm 1318$  pg/mL to  $879 \pm 1138$  pg/mL,  $p = 0.272$ ). The slope was steeper and had statistical significance in VD (+) population but not between groups ( $p=0.221$ ), as depicted in Table 3.

**Table 2:** Characteristics of vitamin D oral intake by the study population.

Variable	Vitamin D supplementation		
	VD (+)*	VD (-)*	p value ¶
	n (%) = 52 (60)	n (%) = 35 (40)	
Supplementation Period (days), median (IQR)	325 (134)	365 (108)	0.079
Monthly Cholecalciferol dosage (IU), median (IQR)	22 400 (77 600)	22 400 (0)	0.325
Poor Adherence to Treatment, n (%)	0 (0)	14 (40)	<0.001

IQR, interquartile range; IU, international units.

\* VD (+) refers to the group that corrected the vitamin D deficiency; VD (-) refers to the group that maintained the vitamin D deficiency.

¶ Chi-square, Fisher's exact test or Mann-Whitney U test, as appropriate.

**Table 3:** Clinical and functional variables at baseline and after 12-month follow-up by cluster

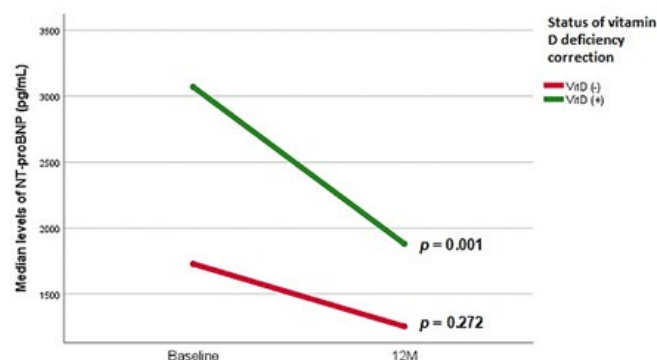
Variable	Baseline			After Vitamin D supplementation		
	VD (+)*	VD (-)*	p value ¶	VD (+)*	VD (-)*	p value ¶
	n (%) = 52 (60)	n (%) = 35 (40)		n (%) = 52 (60)	n (%) = 35 (40)	
<b>Functional class (NYHA), n (%)</b>						
NYHA class I	12 (23)	4 (11)	0,587	16 (31)	6 (17)	0,291
NYHA class II	31 (60)	24 (69)		27 (52)	25 (71)	
NYHA class III	8 (15)	6 (17)		5 (10)	3 (9)	
Non-classifiable	1 (2)	1 (3)		4 (8)	1 (3)	
<b>NT-proBNP in pg/mL, median (IQR)</b>	1740 (2761)	902.50 (1318)	0,221	851 (1436)	879 (1138)	0,211**
<b>HF hospitalizations in the last 12 months, mean (SD)</b>	1.02 (0.67)	1.03 (1.04)	0,604	0.29 (0.82)	0.40 (0.81)	0,656**
<b>6MWD in meters, mean (SD)</b>	314.22 (110.24)	308.27 (101.66)	0,480	335 (121.2)	318.7 (99.8)	0,472**
<b>DASI in points, mean (SD)</b>	24.44 (11.58)	23.86 (11.08)	0,635	24.55 (13.94)	24.29 (10.67)	0,624**

DASI, Duke Activity Score Index; HF, heart failure; IQR, interquartile range; 6MWD, Six-Minute Walking Test Distance; SD, standard-deviation; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide

\* VD (+) refers to the group that corrected the vitamin D deficit; VD (-) refers to the group that maintained the deficit.

\*\* p values for between-groups repeated measures analysis.

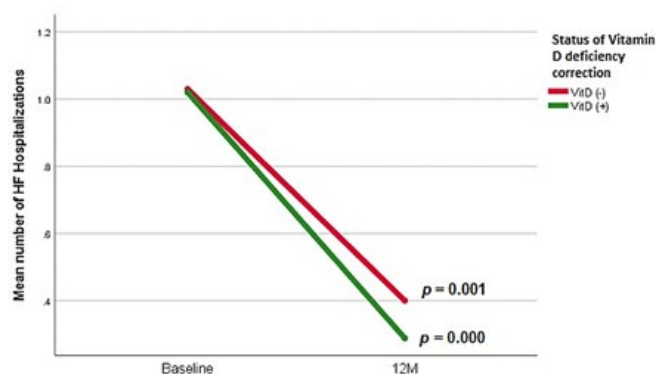
¶ Chi-square, Fisher's exact test, Mann-Whitney U test and one-way ANOVA, as appropriate.

**Figure 2:** Evolution of median NT-proBNP levels in pg/mL before and after vitamin D supplementation therapy for both groups.

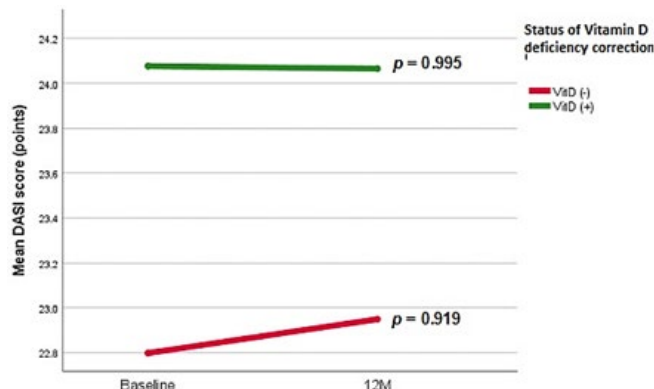
Additionally, there was a statistically significant reduction in the mean number of hHF within both groups; VD (+) group:  $1.02 \pm 0.67$  to  $0.29 \pm 0.82$ ,  $p < 0.001$  vs VD (-) group:  $1.03 \pm 1.04$  to  $0.40 \pm 0.81$ ,  $p = 0.001$  – Fig. 3 – but not between groups ( $p = 0.656$ ) – Table 3.

There was an improvement of 6MWD in the 2 groups; VD (+):  $314.22 \pm 110.24$  m to  $335.00 \pm 121.20$  m,  $p = 0.397$  vs VD (-):  $308.27 \pm 101.66$  m to  $318.70 \pm 99.80$  m,  $p = 0.076$ ) but with no statistical significance, neither within nor between groups – Fig. 4 and Table 3. Several patients were not able to perform the test: 8 patients in VD (+) group and 5 patients in VD (-) group.

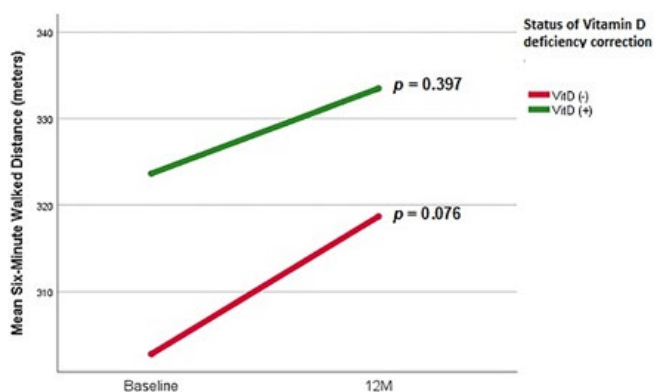
Regarding DASI evolution, we report a slight increase within both groups; VD (+):  $24.44 \pm 11.58$  points to  $24.55 \pm$



**Figure 3:** Evolution of mean number of hospitalizations before and after vitamin D supplementation therapy for both groups.



**Figure 5:** Evolution of mean DASI score before and after vitamin D supplementation therapy for both groups.



**Figure 4:** Evolution of mean distance (in meters) walked on Six-Minute Walking Test Distance; before and after vitamin D supplementation therapy for both groups.

13.94 points,  $p = 0.995$  vs VD (-):  $23.86 \pm 11.08$  points to  $24.29 \pm 10.67$  points,  $p = 0.919$ ), greater in VD (-) population, that was independent of VD deficiency correction status – Fig. 5 and Table 3.

There were no deaths in either group during the follow-up period.

## Discussion

This study reports one-year outcomes of a HF patients' cohort with VD deficiency treated with VD, and it shows that the correction of VD deficiency did not correlate statistically with improvements in functional capacity measured by NYHA class, DASI score or 6MWD neither with reduction of NT-proBNP level or number of hHF.

NYHA classification is a simple and widely-used tool to stratify dyspnea and its impact on daily activities of HF patients, being considered an unreliable predictor of outcome.<sup>13</sup> We found more patients on class I NYHA in both groups at the 12-month evaluation after VD supplementation, which can be considered as an improvement symptom in this population. Patients who corrected VD deficiency showed a statistically significant decrease of NT-proBNP levels over time, within

group effect, that was not seen in patients who did not correct VD deficiency. This result is clinically significant since NT-proBNP is a strong prognostic factor with higher values predicting higher risk of death and hospital readmissions.<sup>14-16</sup> Although, as no difference was seen between groups after one year of VD treatment, the greater decrease of NT-proBNP levels is probably a consequence of others interventions, possibly to a better adherence to drug treatments and non-pharmacological interventions of the VD (+) group of patients.

Vitamin D deficiency has been shown that correlates with an increased risk of hHF in various studies and, independently, with higher overall mortality, but some randomized studies failed to show an impact of VD supplementation on mortality of HF patients.<sup>1,3,5,6,10,17-19</sup> One of these studies is the EVITA study<sup>17</sup> that evaluated a very distinct HF population, mainly male, two decades younger than those of the present study and with reduced LVEF, waiting for heart transplantation. Notwithstanding, the significant reduction in hHF over time that we found in both groups, could reflect the impact of the multidisciplinary care in preventing such events, since we did not find any correlation between hHF and normalization of VD levels and research shows that interventions with VD did not reduce the first hospitalization rate in heart failure.<sup>20</sup>

DASI has been validated as a functional tool with prognostic implication in stable HF patients.<sup>19,21</sup> Likewise, 6MWD has been considered a highly reliable and independent predictor of hospitalization and mortality in chronic HF patients.<sup>22,23</sup> We found no impact of VD deficiency correction in these functional tests. The 6MWD results could have been influenced by the fact of several patients not being able to perform the test. However, the change in 6MWD between baseline and 12 months after VD supplementation was the primary endpoint of the VINDICATE study, which was also neutral.<sup>11</sup>

Overall, we found a functional and clinical improvement in both groups over time that may be due to a regular follow-up in a multidisciplinary HF clinic and the consequent optimization of HF care. The effect of VD supplementation in hHF, 6MWD and NT-proBNP was neutral, in line with the overall results of

the previous studies.<sup>11,24</sup> Although the association between VD deficiency and poor outcome seems real, the supplementation did not seem to have impact in the usual outcomes of the HF trials, supported by study that demonstrated that VD supplementation of VD-sufficient subjects does not provide any benefit in terms of cardiovascular health in general population.<sup>25</sup> Probably, the VD deficiency in HF patients reflects advanced disease and poor overall health status that do not change by correcting VD levels.<sup>12,24</sup>

Ejection fraction (EF) after treatment was not evaluated in this study, which could be an overall relevant data, since study results indicate that prescribing VD for patients with HF, especially in LVEF < 50%, enhances myocardial EF.<sup>26</sup>

This study has limitations. First, the retrospective nature and consequent difficulty to control adherence to VD treatment. Second, the exclusion of a relevant number of non-followed-up patients which reduced considerably the number of study patients. In spite of these, we expect to highlight an underexplored topic and to trigger future randomized prospective studies with larger populations in order to achieve more conclusive results.

## Conclusion

The correction of VD deficiency in this population of HF patients did not have impact in NYHA class, NT-proBNP levels, hHF, DASI score or 6MWD. The improvements reported within both groups may reflect the impact of a HF clinic optimized care. Randomized prospective studies with larger populations are needed in order to achieve more conclusive results. ■

## Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial. Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of

Ethics of the World Medical Association (Declaration of Helsinki).

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