Heart Failure Treatment at Hospital Discharge. Do we Adhere to Guidelines? A Sub-analysis of the ARGEN-IC Registry

Tratamiento al alta en insuficiencia cardiaca ¿cumplimos con las guías? Subanálisis del registro ARGEN-IC

NICOLÁS CARUSO[1,], PAULA PEREZ TERNS[1], JULIETA SORICETTI[1,], GUILLERMO BORTMAN[1,], MARÍA LORENA CORONEL[2], ANALÍA BENAVIDEZ[1,], ALFREDO HIRSCHON PRADO[1], HERNÁN COHEN ARAZI[1,], ALBERTO FERNÁNDEZ[1,], ADRIÁN LESCANO[1,]

ABSTRACT

Background: Heart failure (HF) can be classified in different ways. The most used classification is based on left ventricular ejection fraction (LVEF) and involves groups with therapeutic options that impact on morbidity and mortality. The information about adherence to the recommendation of specific treatment at hospital discharge for HF comes from other countries but not ours.
Objectives: To evaluate the prescription of specific drugs for HF with reduced LVEF (HFrEF) at discharge in hospitalized patients for acute heart failure (AHF), as well as the clinical parameters related to the indication.
Methods: Patients with diagnosis of AHF incorporated to the prospective ARGEN-IC registry were included. Reduced LVEF was defined as that ≤ 40%. Prescription rate of drugs recommended for HFrEF at discharge and its association with clinical parameters was analyzed. Data was incorporated to the Survey Monkey electronic database and analyzed using STATA® software package. The Student's t test or chi-square test were used, as applicable.
Results: A total of 871 patients were included; mean age was 68.1 years and 72.4% were men. LEVF was reduced in 53.3%. Length of hospital stay was 8 days (IQR 5-12) and mortality rate was 7.32%. At discharge, systolic blood pressure was > 130 mm Hg in 12.6% of the patients and 64.4% had heart rate > 70 beats per minute; 22.5% were discharged without beta-blockers, 29.1% without vasodilators and 43.7% without aldosterone antagonists. Comorbidities included chronic obstructive pulmonary disease (COPD) in 12.6%, glomerular filtration rate < 30 mL/min in 12.5 %, serum creatinine > 2.5 mg/dL in 8,9% and hyperkalemia in 0.44%.
Conclusions: We documented suboptimal prescription rate and poor adherence to the recommendations; thus, it is extremely important to implement strategies to change the reality in our region.

Key word: Heart Failure / therapy - Patient Discharge - Contraindications - Argentina - Registries

RESUMEN

Introducción: La insuficiencia cardiaca (IC) se puede clasificar de diferentes maneras. La más utilizada, según la fracción de eyección ventricular izquierda (FEVI), distingue a grupos con opciones terapéuticas que impactan en la morbimortalidad. Existe información sobre adherencia a las recomendaciones de tratamiento específico al alta de la internación por IC en otros países, pero carecemos de ésta en el nuestro.
Objetivos: Evaluar la prescripción de drogas específicas para IC con FEVI reducida (ICFER) al alta de pacientes internados por insuficiencia cardiaca aguda (ICA), así como los parámetros clínicos relacionados con la indicación.
Materiales y métodos: Pacientes incorporados al registro prospectivo ARGEN-IC, con diagnóstico de ICA. Se definió FEVI deteriorada a la ≤40%; se analizó la prescripción de drogas recomendadas para ICFER al alta, y su relación con parámetros clínicos. Datos incorporados a la base Survey Monkey y analizados con el programa STATA 14. Se utilizó el test de t o chi cuadrado según la variable utilizada.
Resultados: 871 pacientes incluidos, edad 68,1 años y 72,4% varones. FEVI reducida en el 53,3%. La estadía hospitalaria fue 8 días (RIC 5-12) y la mortalidad 7,32%. El 12,6% egresó con tensión arterial sistólica >130 mmHg y el 64,4% con frecuencia cardíaca >70 latidos por minuto. El 22,5% egresó sin betabloqueantes, el 29,1% sin vasodilatadores y el 43,7% sin antialdosterónicos. Entre las probables contraindicaciones, observamos 12,6% de enfermedad pulmonar obstructiva crónica (EPOC), 12,5% de índice de filtrado glomerular menor de 30 ml/min, 8,9% de creatinina mayor de 25 mg/dL y 0,44% hiperkalemia.
Conclusiones: Constatamos prescripción subóptima y pobre cumplimiento de las recomendaciones; por ello es de vital importancia implementar estrategias para cambiar la realidad en nuestra región.

Palabras clave: Insuficiencia cardíaca / tratamiento - Alta del paciente - Contraindicaciones - Argentina - Registros

INTRODUCTION

Heart failure (HF) represents a universal public health problem due to multiple causes, including increasing age of the population and greater availability of treatments for different diseases which prolong patients' survival, resulting in a higher prevalence of cardiovascular diseases, such as HF, in elder patients. (1-3)

Fortunately, the pathophysiology of HF is better understood, and there are better diagnostic methods and pharmacological and non-pharmacological treatments which have made HF one of the syndromes with the greatest therapeutic progress in recent years. The higher survival of patients is associated with an exponential increase in health care costs worldwide. (4-6)

Nevertheless, the rate of events (HF rehospitalizations, mortality) continues to be unacceptably high despite all the progress made, especially in the early post-discharge period, termed the "vulnerable phase" of HF. Different registries worldwide have shown poor results in this regard despite some progress (rehospitalization rates of 15% and 35% at 30 and 60 days after discharge, respectively). (7,8)

The different scientific societies suggest the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers and aldosterone antagonists in all patients with HF with reduced ejection fraction (rEF), and without contraindications for their use, since they have demonstrated reduction in morbidity and mortality in this group of patients. (9,10) Despite these recommendations, the use of specific medication in different registries is relatively low and a large proportion of patients (about 70%) are medicated with different doses of diuretics in the outpatient phase but not with disease-modifying drugs that reduce mortality. (11-13)

As this information has major relevance in the prognosis of our patients, it is essential to acknowledge the prescription rate of specific drugs and their doses at discharge. In this setting, we decided to analyze these data in the population of the Argentine Registry of Heart Failure, ARGEN-IC.

METHODS

A national, descriptive, prospective multicenter registry was performed including the information provided by 50 health care centers from August 2018 to March 2019. These centers participated voluntarily of the survey generated by the Research Area and the Heart Failure and Pulmonary Hypertension Council and approved by SAC Ethics Committee. (14)

The study included patients > 18 years with confirmed acute heart failure (AHF) who accepted and signed the informed consent. Those patients with left ventricular ejection fraction (LVEF) measured before or during hospitalization were included in the present analysis. Patients with ST-segment elevation acute myocardial infarction, sepsis on admission, and psychiatric or physical conditions that limit-ed follow-up were excluded from the analysis. The variables associated with demographic and clinical data, diagnostic methods, therapeutic interventions, in-hospital outcome, parameters at discharge and events during follow-up were recorded.

Presentation, etiologies, precipitating factors and in-hospital outcome were defined by the investigators according to the international recommendations. Heart failure with reduced ejection fraction (HFrEF) was considered when LVEF was ≤ 40%. The present analysis was carried out within this subgroup to evaluate the hemodynamic variables and medical treatment at hospital discharge.

Data were collected through a closed questionnaire (Survey Monkey electronic database) and the information was monitored by an event and data committee. Events of interest were defined according to guidelines and recommendations. The information analyzed included comorbidities, prior medical treatment and at discharge, and control of clinical variables, including heart rate (HR) and systolic blood pressure (SBP) at discharge. Uncontrolled SBP at discharge was defined as > 130 mm Hg. Elevated HR was defined as > 70 beats per minute (bpm). The presence of comorbidities or absolute or relative contraindications that could reduce the indication of specific medication for HFrEF was also evaluated.

Data monitoring

The registry data were verified with the original documents in 20% of patients by specially trained staff.

Statistical analysis

Qualitative variables are presented as percentages. Quantitative variables are expressed as mean and standard deviation or median and interquartile range (IQR), according to their distribution. Student's t, chi-square, Wilcoxon or Mann Whitney tests were used for statistical analysis according to the type of variable and distribution. A p value <0.05 was considered statistically significant. All the statistical calculations were performed using STATA 14 software package.

Ethical considerations

The protocol was approved by the Committee on Ethics of the Argentine Society of Cardiology.

RESULTS

Of 910 patients entered in the registry, LVEF was reported in 871, from 18 provinces and 50 health care centers, 78% from the Autonomous City of Buenos Aires (CABA). These patients were included in the analysis. Thirty-eight percent of the patients had private health insurance as medical coverage. Mean LVEF was 41% (SD 15.4), 53.3% (n = 464) had reduced LVEF while 46.7% (n = 407) had intermediate or preserved LVEF. In the subgroup of patients with HFrEF, mean age was 68.1 years (SD 14.2) and 72.4% were men. In patients with LVEF > 40%, mean age was 76.4% (SD 13.1%) and 45.9% were men (p < 0.001 for both variables). The percentage of patients who had received influenza vaccine and pneumococcal vaccine was 32.3% and 24.1%, respectively, and was similar to that of patients with LVEF > 40%. Median length of hospital stay was 8 days (5-12); in-hospital mortality was 7.32% without significant differences with the group with higher LVEF (Table 1).

Table 2 describes the associated comorbidities; diabetes (33.1%), history of myocardial infarction (21.5%) and dyslipidemia (41,1%), and these conditions were more prevalent than in in patients with LVEF > 40%. The presence of atrial fibrillation (25.4%) and hypertension (HTN, 68.8%) was less common in the group with reduced LVEF. The prevalence of Chagas disease was 2.5%.

The percentage of patients with chronic kidney disease (CKD) was 18.3%; 9.3% were obese and 12.9% had chronic obstructive pulmonary disease (COPD), with no significant differences in the group with preserved LVEF (Table 2).

Table 3 shows the use of oral drugs recommended in patients with reduced LVEF on admission and discharge. On admission, 63.1% were receiving beta-blockers, 59.1% ACE inhibitors, ARBs or ARNIs and 35.1% aldosterone antagonists. Prescriptions at the time of hospital discharge included beta-blockers in 77.5% of patients, ACE inhibitors in 44.2%, ARBs in 16.6%, ARNIs in 10.1%, and aldosterone antagonists in 56.3%. These data show a significant increase in the prescription rate of all these drugs compared with the period preceding admission. Daily doses of the medications prescribed at discharge are described in Table 4. In addition, 71.3% was discharged with indication of furosemide, with a mean dose of 59.5 mg/day.

We also analyzed the proportion of patients with controlled and uncontrolled blood pressure and heart rate. At hospital discharge, SBP was uncontrolled in 12.6% of the patients and 64.4% had elevated heart rate; one of both variables was uncontrolled in 67.8 % (Figure 1).

Finally, the possible causes for not prescribing drugs with high level of recommendation were COPD in 12.6%, serum creatinine > 2.5 mg/dL in 8.9%, and glomerular filtration rate < 30 mL/min in 12.5%. The prevalence of hyperkalemia (defined as serum potassium levels > 5.5 mEq/L) was 0.44%.

DISCUSSION

The ARGEN-IC registry analyzed 871 patients with complete data, which represents the highest recruitment of patients compared with other acute HF registries performed by the SAC. (8,9) Most patients were included in CABA (78%), with a predominance of private health insurance coverage (38%), which may not be strictly representative of the Argentine population, and may represent an important inclusion bias, since centers specialized in the management of HF voluntarily included patients in this registry.

We observed a heterogeneous population with reduced LVEF, relatively young for this condition (68.1 years) and with a predominance of male sex (72.4%), generating a representative sample for the analysis and in agreement with other cohorts. In addition, it constitutes a younger population with a higher prevalence of men than the subgroup with LVEF > 40%, a finding also observed in other registries. (15,16) In our population, mortality and length of hospital stay

Table 1. Baseline characteristics, length of hospital stay and in-hospital mortality

	LVEF > 40 (%) n = 407	LVEF ≤ 40 (%) n = 464	P value
Age, years (±SD)	76.4 (±13.1)	68.1 (±14.4)	< 0.001
Men, %	45.9	72.4	< 0.001
Length of hospital stay, days (IQR)	7 (5-12)	8 (5-12)	0.56
In-hospital mortality, %	7.4	7.3	0.98
Previous vaccination, %			
Influenza	36.3	32.3	0.21
Pneumococcus	28.0	24.1	0.19

LVEF: left ventricular ejection fraction. SD: standard deviation. IQR: interquartile range

Table 2. Risk factors and associated comorbidities

Clinical characteristics	LVEF > 40 % n = 407	LVEF ≤ 40% n = 464	P value
Hypertension	80.8	68.8	0.003
Dyslipidemia	33.1	41.1	0.015
Smoking habits	26.7	34.1	0.02
Diabetes	29.2	33.1	0.2
Chronic atrial fibrillation	36.8	25.4	< 0.001
Previous MI	12.7	21.5	< 0.001
Chagas' disease	0.7	2.5	0.036
CKD	17.9	18.3	0.88
Obesity	9.8	9.3	0.77
COPD	15.9	12.9	0.20

LVEF: left ventricular ejection fraction, MI: myocardial infarction
CKD: chronic kidney disease. COPD: chronic obstructive pulmonary disease

	Before hospitalization	At hospital discharge	p value
Beta-blockers, %	63.1	77.5	< 0.001
ACE inhibitors, ARBS, ARNIs, %	59.5	70.9	< 0.001
Aldosterone antagonists, %	35.1	56.3	< 0.001
Furosemide, %	48.5	71.3	< 0.001

**Table 3.** Prescription of specific drugs on admission and discharge

ACE: angiotensin-converting enzyme. ARB: angiotensin II receptor blocker
ARNI: angiotensin receptor-neprilysin inhibitors

Table 4. Dose of medication prescribed at discharge (the values are expressed as median and interquartile range)

Dose (mg/day)		% of patients with target dose
Beta-blockers		
Carvedilol	12.5 (6.25-25)	8.2
Bisoprolol	5 (2.5-5)	18.1
Nevibolol	5 (3.125-5)	8.3
Metoprolol	50	0
ACE inhibitors/ARBs, ARNIs		
Enalapril	10 (5-10)	16.4
Losartan	50 (50-100)	0
Valsartan	160 (80-160)	8
Candesartan	12 (8-32)	0
Sacubitril Valsartan	100 (50-100)	4.4
Aldosterone antagonists		
Spironolactone	25 (25-25)	15.2
Eplerenone	25 (25-25)	19.6
Furosemide	40 (40-80)	

ACE: angiotensin-converting enzyme
ARB: angiotensin II receptor blocker
ARNI: angiotensin receptor-neprilysin inhibitors
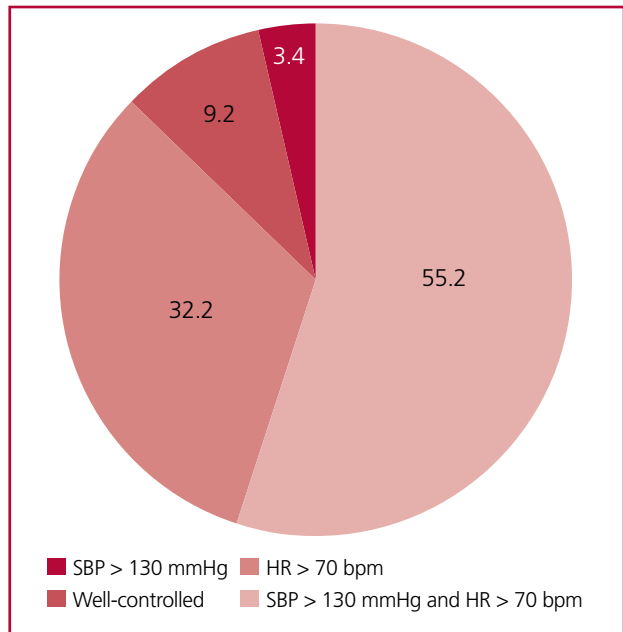
Fig. 1. Heart rate (HR) and systolic blood pressure (SBP) controlled at discharge (%)

in patients with reduced LVEF were similar to that of the general population. Therefore, LVEF did not represent a variable with impact on in-hospital mortality.

When we analyzed medical treatment before hospitalization, we found that a significant percentage of patients were receiving ACE inhibitors, ARBs or ARNIs, beta-blockers and aldosterone antagonists, and hospitalization was an opportunity to initiate specific treatment. Nevertheless, although prescription rate was significantly higher, the percentage of patients with specific drugs was insufficient at discharge. Therefore, 22.5% were discharged without beta-blockers, 29.1% without ACE inhibitors, ARBs or ARNIs and 43.7% without aldosterone antagonists. (Table 3). In addition, all the drugs were prescribed in suboptimal doses. We should keep in mind that the different guidelines recommend higher target doses of all drugs for these patients (enalapril 20-40 mg/day, losartan 150 mg/day, valsartan 320 mg/day, candesartan 32 mg/day, bisoprolol 10 mg/day, carvedilol 50 mg/day, metoprolol 200 mg/day, nebivolol 10 mg/day, valsartan/sacubitril 400 mg/day and spironolactone or eplerenone 50 mg/day). (9,10) Unfortunately, the AR-

GEN-IC data are consistent with those of the different registries worldwide, irrespective of the sociocultural characteristics of each country. The 2013 European Society of Cardiology registry of hospitalizations for AHF showed that hospitalization also contributed to increase the prescription of specific drugs, although the prescription rate at discharge was similar to the one described by our group, with 77% of ACE inhibitors or ARBs, 71.8% of beta-blockers and 55.3% of aldosterone antagonists, and 70-80% of patients with suboptimal doses. (17) This is particularly relevant, considering that the US OPTIMIZE-HF registry demonstrated that the lack of prescription of ACE inhibitors/ARBs and beta-blockers is an independent predictor of mortality during post-discharge follow-up. (18) It should be noted that the global trend shows that the prescription rate tends to increase after discharge during outpatient follow-up. This trend was demonstrated by the Spanish registry in 2015 and CHECK-HF in 2019, with a prescription rate of ACE inhibitors/ARBs and beta-blockers > 80%. (19, 20) In conclusion, considering that adherence to recommendations will have a favorable impact in terms of events for our patients,

(21, 22) and that although prescription rate usually increases during follow-up, we should make the most of hospital discharge to achieve the highest possible adherence to specific therapy.

Most HF registries involve physicians from different specialties, as the sub-analysis of the ADHERE registry demonstrated. (23) However, most of the participating centers in the ARGEN-IC registry corresponded to cardiology departments with experience in the management of AHF. This situation may be worrisome, as it questions medical knowledge about how much benefit these drugs provide in terms of survival or reflects the inability of the medical community to manage the adverse effects of these drugs. Moreover, we can assume that this situation is not justified by the presence of contraindications or precautions, since their prevalence was very low (12.6% of COPD, 12.5% of kidney dysfunction and 0.4% of hyperkalemia), even lower than in other HF registries.

Although hospitalization did not change the average daily dose of furosemide (average dose on admission 58.6 mg/day, and at discharge 59.5 mg/day), the percentage of patients treated with furosemide was significantly higher at discharge than on admission, and this prescription rate seems to be high (48.5% on admission vs 71.3% at discharge). Although the use of loop diuretics was associated with adverse outcomes in HF, it may probably be a marker of more severe disease. (24) In this regard, there is an association between dose and greater risk of hospitalizations, mortality due to worsening HF, all-cause mortality or sudden death. Consequently, the fact that more than two-thirds of the patients are discharged with high dose of diuretics and that the prescription rate and dose of specific mortality-modifying medication is so low, is a negative aspect of the study. This is a relevant issue to consider, as many experts suggest reducing loop diuretics to achieve better titration of specific medications. In this regard in the PARADIGM-HF study, patients who benefited from treatment with sacubitril/valsartan received lower doses of loop diuretics compared with the enalapril group. These results suggest the importance of adjusting the dose of diuretics before starting disease-modifying treatment, more precisely ARNIs. (25,26)

One argument against the widespread use of specific medication may be related to costs. In this regard, we want to emphasize that all the interventions that reduce hospitalizations in HF have demonstrated to be cost-effective; therefore, cardiologists should not limit their prescription, when these drugs are indicated. (5,6)

Study limitations

Although the ARGEN-IC registry is the argentine acute HF registry with the largest number of patients included, the sample may not be representative due to the participation of heart failure centers and by the high recruitment of centers in CABA. The reasons for not prescribing specific medication and for not attaining the target dose (contraindications, adverse effects or medication still being titrated) were not recorded.

CONCLUSIONS

The ARGEN-IC registry includes a heterogeneous population, with advanced mean age and several comorbidities. Suboptimal prescription rates of medications with impact on morbidity and mortality was observed in the subgroup of patients with reduced LVEF. Even more, those patients treated with specific medication were receiving suboptimal doses, despite the lack of contraindications or clear reasons for not following recommendations with high level of evidence. These findings highlight the need for analyzing the causes and implementing educational strategies to change the course of disease.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

REFERENCES

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93: 1137–46.https://doi.org/10.1136/hrt.2003.025270
2. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JCM, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004;25:1614–9. https://doi.org/10.1016/j.ehj.2004.06.038
3. Ceia F, Fonseca C, Mota T, Morais H, Matias F, De Sousa A, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail 2002;4:531–9. https://doi.org/10.1016/S1388-9842(02)00034-X
4. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65-75. https://doi.org/10.1093/eurheartj/ehi555
5. Jackson S, Tong X, King R, Loustalot F, Hong Y, Ritchey M. National Burden of Heart Failure Events in the United States, 2006 to 2014. Circ Heart Fail 2018;11:e004873. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004873
6. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. BMC Cardiovasc Disord 2018;18:74. https://doi.org/10.1186/s12872-018-0815-3
7. Gheorghiade M, Vaduganathan M, Fonarow G, Bonow R. Rehospitalization for Heart Failure. J Am Coll Cardiol 2013;61:391-40. https://doi.org/10.1016/j.jacc.2012.09.038
8. Greene S, Fonarow G, Vaduganathan M, Khan S, Butler J and Gheorghiade M. The vulnerable phase after hospitalization for heart failure. Nat. Rev. Cardiol 2015;12:220-9. https://doi.org/10.1038/nrcardio.2015.14
9. Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, Coats A, Falk V. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–200. https://doi.org/10.1093/eurheartj/ehw128
10. Marino J, Barisani JL, Thierer J, Liniado G, Pereiro SM, Francesia A. Consenso de insuficiencia cardiaca crónica. Sociedad Argentina de Cardiología. Rev Argent Cardiol 2016;84(Supl 3.):1-50.
11. Rizzo M, Thierer J, Francesia A, Bettati MI, Pérez Terns P, Casas M. Registro Nacional de Internación por Insuficiencia Cardíaca 2002-2003. Rev Argent Cardiol 2004;72:333-40.
12. Fairman E, Thierer J, Rodríguez L, Blanco P, Guetta J, Fernández S, et al. Registro Nacional de Internación por Insuficiencia Cardiaca 2007. Rev Argent Cardiol 2009;77:33-9.
13. Gheorghiade M. and Filippatos G. Reassessing treatment of

acute failure syndromes: The ADHERE Registry. Eur Heart J 2005;7suppl.B):13–9. https://doi.org/10.1093/eurheartj/sui008

14. Lescano A, Sorasio G, Soricetti J, Arakaki D, Coronel L, Cáceres L et al. Registro Argentino de Insuficiencia Cardíaca Aguda (ARGEN-IC). Evaluación de cohorte parcial a 30 días. Rev Argent Cardiol 2020;88:118-25. https://doi.org/10.7775/rac.es.v88.i2.17201

15. Maggioni AP, Dahlstro¨m U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013;15:808–17. https://doi.org/10.1093/eurjhf/hft050

16. Pocock SJ, Ariti CA, McMurray JJV, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34: 1404–13. https://doi.org/10.1093/eurheartj/ehs337

17. Maggioni A, Anker S, Dahlstrom U, Filippatos G. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173–84. https://doi.org/10.1093/eurjhf/hft134

18. O'Connor C, Abraham W, Albert N, Clare R. Predictors of mortality after discharge in patients hospitalized with heart failure: An analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2008;156:662-7.

19. Crespo-Leiro,M, Segovia-Cubero J, Gonzalez-Costello, J, Bayes-Genis A. Adherence to the ESC Heart Failure Treatment Guidelines in Spain: ESC Heart Failure Long-term Registry. Rev Esp Cardiol 2015;68:785–93. https://doi.org/10.1016/j.recesp.2015.03.008

20. Brunner-La Rocca HP, Linssen G, Smeele F. Contemporary Drug Treatment of Chronic Heart Failure with Reduced Ejection Fraction. The CHECK-HF Registry. JACC Heart Fail 2019;7:13-21. https://doi.org/10.1016/j.jchf.2018.10.010

21. Komajda M, Cowie M, Tavazzi L, Ponikowski P. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Failure 2017;19:1414–23. https://doi.org/10.1002/ejhf.887

22. Komajda M, Schöpe J, Wagenpfeil S, Tavazzi L. Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail 2019;21:921–9. https://doi.org/10.1002/ejhf.1459

23. Fonarow G, Yancy C, Heywood T. Adherence to Heart Failure Quality-of-Care Indicators in US Hospitals. Analysis of the AD-HERE Registry. Arch Intern Med 2005;165:1469-77. https://doi.org/10.1001/archinte.165.13.1469

24. Yilmaz MB, Gayat E, Salem R, Lassus J, Nikolaou M, Laribi M, et al. Impact of diuretic dosing on mortality in acute heart failure using a propensity-matched analysis. Eur J Heart Fail 2011;13:1244-52. https://doi.org/10.1093/eurjhf/hfr121

25. Vardeny O, Claggett B, Kachadourian J, Desai A, Packer M, Rouleau J, et al.Z. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. Eur J Heart Fail 2019;21:337–41. https://doi.org/10.1002/ejhf.1402

26. Beck-da-Silva L, Rohde L. The Diuretic Effect of Sacubitril/Valsartan Might Be Clinically Relevant. Arq Bras Cardiol 2019;112:791-2. https://doi.org/10.5935/abc.20190080