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JOÃO DOMINGUES VAZ

Medicines for Reduced Ejection Fraction Heart Failure in Central Region of Portugal´s Primary Care: a 2022 observational study

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Medicação da insuficiência cardíaca com fração de ejeção reduzida, nos cuidados primários da região centro de Portugal: um estudo observacional de 2022

Medicines for reduced ejection fraction heart failure in central region of Portugal´s primary care: a 2022 observational study

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LIST OF ABBREVIATIONS

‘ESC’ European Society of Cardiology

‘GP’ General Pactitioners

‘LVEF’ Left Ventricular Ejection Fraction

‘CHF’ Heart failure

‘CCHF’ Chronic Heart failure

‘CHFrEF’ Heart failure with reduced Ejection Fraction

‘PCHF’ Patients with CHF

‘ICPC-2’ International Classification for Primary Care-2

‘RAAS’ Renin–Angiotensin–Aldosterone System

‘SGLT2-I’ Sodium–Glucose Cotransporter-2 Inhibitors

‘ARNI’ Angiotensin Receptor–Neprilysin Inhibitors

‘MRA’ Mineralocorticoid Antagonists

‘BB’ Beta-Blockers

‘ACE-I’ Angiotensin Conversion Enzyme-Inhibitor

‘ARB’ Angiotensin 2 Receptor Antagonists

ABSTRACT

Introduction

Chronic heart failure (CHF) is an ongoing debilitating disease associated with high mortality and frequent hospitalizations, mostly managed by primary care physicians (PCPs). Despite the European Society of Cardiology (ESC) guidelines, standard prognostic CHF therapeutic recommendations can be underutilized. Therefore, the present study aims to evaluate the accordance of the prognostic medicines therapy in adults diagnosed with Chronic Heart Failure with Reduced Ejection Fraction (CHFrEF) currently performed in primary health care centers in central Portugal, with the most recent guidelines issued by the European Society of Cardiology (ESC).

Methods

Observational, cross-sectional study in a population of 2381 persons diagnosed with Chronic Heart Failure (CHF) from which those with CHFrEF (P-CHFrEF) were studied in a proportional random size representative sample, 95% confidence interval and 5% error margin, using the inverted alphabetical order list in the 31st December 2021. Age, gender, year of International Classification for Primary Care-2 (ICPC-2, K-77) problem classification, years since the last echocardiogram, ongoing prognostic modifying medicines therapy for CHFrEF and other drugs relevant to CHF treatment were gathered. Data were obtained from 11, conveniently invited Primary Health Care Units, that joined the study, by General Practice/Family Medicine internees, after an Ethics Committee positive decision.

Results

A sample of 133 patients was studied, treatment with a renin–angiotensin system (RAAS-I) ongoing in 91.0%, beta-blockers (BB) in 75.2 %, Mineralocorticoid Antagonists (MRA) in 40.6% and inhibitors of the Sodium-glucose Cotransporter-2 (SGLT2-I) in 44.4%. The optimized medical quadruple therapy was verified in 28 patients (21.1%), and in 38 (28.6 %) three prognostic modifying drugs were prescribed.

Discussion

The prognostic modifying treatments according to the ESC most recent guidelines were underused particularly regarding the prescription of combination regimens. Despite individual prescription rates of the prognostic modifying drug classes being significantly higher in comparison with other previous studies, there is still space for improvement. Our findings may

reflect the impact multimorbidity and lack of an implemented framework have in the prescription regimens.

Conclusion

Prognostic modifying medicines according to the ESC most recent guidelines were underused for 50.4% of the P-CHFrEF, improvement still being necessary. A reflection on the barriers physicians encounter to be in accordance with the guidelines in patients with multimorbidity must be made.

Key words: Chronic Heart Failure, Chronic Heart Failure with Reduced Ejection Fraction, General practice, Medicines, Pharmacotherapy

RESUMO

Introdução

A insuficiência cardíaca crónica (ICC) é uma doença debilitante contínua associada a alta mortalidade e hospitalizações frequentes, sendo gerida principalmente por médicos associados a cuidados de saúde primários. Apesar das diretrizes da European Society of Cardiology (ESC), as recomendações terapêuticas prognósticas para ICC podem ser subutilizadas. Assim, o presente estudo tem como objetivo avaliar a concordância da terapêutica farmacológica prognóstica da ICC em adultos com diagnóstico de Insuficiência Cardíaca Crónica com Fração de Ejeção Reduzida (ICCFEr), inserida à data de realizada nos centros de saúde primários da região centro de Portugal, com as mais recentes diretrizes da European Society of Cardiology (ESC).

Métodos

Estudo observacional, transversal numa população de 2381 pessoas diagnosticadas com Insuficiência Cardíaca Crónica (ICC), a partir da qual aqueles com fração de ejeção reduzida ICCFEr (P-ICCFEr) foram estudados numa amostra representativa de tamanho proporcional, intervalo de confiança de 95% e margem de erro de 5%, usando a lista ordinal original invertida por nome em 31 de dezembro de 2021. Idade, sexo, ano de diagnóstico a partir da data da introdução da Classificação Internacional para Cuidados Primários-2 (ICPC-2), anos desde o último ecocardiograma, terapia farmacológica modificadora de prognóstico para ICCFEr prescrita e outros medicamentos relevantes para o tratamento da ICC. Os dados foram obtidos em 11 Unidades de Saúde Familiar, convenientemente convidadas, que aderiram ao estudo, por Internos de Medicina Geral e Familiar, após parecer positivo da Comissão de Ética.

Resultados

Foi estudada uma amostra de 133 pessoas, o tratamento com bloqueador do sistema renina-angiotensina (SRA) estando prescrito em 91.0%, com betabloqueantes (BB) em 75.2%, com antagonistas dos mineralocorticóides (ARM) em 40.6% e com inibidores do cotransportador sódio-glucose 2 (iSGLT2-I) em 44.4% dos pacientes. A terapêutica quádrupla otimizada foi verificada em 28 pacientes (21.1%), estando 38 (28.6%) com três medicamentos modificadores de prognóstico.

Discussão

Os tratamentos modificadores de prognóstico de acordo com as diretrizes mais recentes da ESC estavam subutilizados, principalmente no que diz respeito à prescrição de regimes combinados. Apesar das taxas de prescrição individual das classes de drogas modificadoras de prognóstico serem significativamente maiores em comparação com outros estudos anteriores, ainda há espaço para melhorias. Os nossos achados podem refletir o impacto que a multimorbidade e a falta de uma estrutura implementada têm nos regimes de prescrição.

Conclusão

Os tratamentos modificadores de prognóstico de acordo com as diretrizes mais recentes da ESC para a ICCFEr, estavam subutilizados em 50.4%, havendo espaço para melhorias. É necessária reflexão acerca das barreiras que os médicos encontram no esforço para aplicar as diretrizes em pacientes com multimorbilidade.

Palavras chave: Insuficiência Cardíaca; Insuficiência Cardíaca Crónica com Fração de Ejeção Reduzida; Medicina Geral e Familiar, Medicamentos, Tratamento

INTRODUCTION

Chronic Heart failure (CCHF) is a condition of cardiac functional impairment with numerous etiologies, pathophysiologies, and clinical presentations, where the heart is incapable of maintaining a cardiac output that is adequate to meet metabolic requirements and accommodate venous return (1,2).

Patients with CHF (PCHF) experience a multiplicity of symptoms with a significant impact on their quality of life, including dyspnea, cough, and wheezing from pulmonary congestion, and peripheral edema and ascites from impaired venous return. Constitutional symptoms such as nausea, lack of appetite, and fatigue are also common (1,3).

This clinical syndrome is a substantial public health problem affecting 37.7 million individuals worldwide which carries a 50% 5-year mortality rate and is responsible for over one third of all deaths from cardiovascular causes (2,3). In Portugal, the EPICA study showed that CCHF has a global estimated prevalence of 4.4% amongst adults older than 25 years and 78% have at least two hospital admissions per year, leading to an annual cost around 2.6% of total public health expenditure, and this is expected to increase in the future. (1,4,5)

CHF has been divided into distinct phenotypes based on the measurement of left ventricular ejection fraction (LVEF), three different groups being classified: CHF with reduced ejection fraction (CHFrEF) defined as LVEF ≤40%, CHF with mildly reduced ejection fraction (CHFmrEF) defined as LVEF between 41% and 49% and CHF with preserved ejection fraction (CHFpEF) defined as LVEF ≥50%(6). In this study we will only select and approach PCHF patients who already have an established diagnosis of CHFrEF the P-CHFrEF.

Over the last decades, cardiac remodeling attenuation has been the treatment objective and a standard of care in CHF (7) since the pathological left ventricular (LV) remodeling and consecutive dilatation are the most well described hallmarks of CHFrEF pathogenesis (6,8). During the past 20 years, the benefit of angiotensin-converting enzyme (ACE-I) inhibitors and beta-blockers (BB) on mortality, morbidity and hospitalization of patients with CHF has been demonstrated, and these drugs are strongly recommended in the guidelines (4).

Recently, novel medicines therapies targeting different pathways involved in the pathophysiology of CHFrEF, namely angiotensin receptor–neprilysin inhibitors (ARNI) and

sodium–glucose cotransporter-2 inhibitors (SGLT2-Ii), stood out at an exciting rate, increasingly becoming a part of the contemporary pillars of P-CHFrEF management (6,9).

Despite the release of new guidelines by the European Society of Cardiology (ESC), similar to other medical societies and organizations, CHF therapeutic recommendations are still probably often underutilized, not all PCHF being optimally treated, particularly in primary health care (PHC) setting (4). Under-treatment or clinical inertia, low adherence to guidelines by physicians and low drug compliance by patients are frequently associated to the fact that despite major advances in the management of CHF, morbidity and mortality remain important (10).

PHC plays a vital role in the management of PCHF, more than half of PCHF being diagnosed in PHC centers and almost a third being treated exclusively by GPs (8). Despite numerous reports on CHF in hospital settings, there are few studies on how patients in PHC are being managed and treated (11) Within the Portuguese National Health Service PHC Units can be named UCSP or USF according to structural and organizational setting.

It is therefore relevant to assess the agreement of the currently performed medicines therapy in PCHF with the most recent guidelines, to understand the reasons for the therapeutic non-conformity and to design tactics to overcome it (1).

PCHF can have multimorbidity, its knowledge about the clinical syndrome and its relative importance, comparing it to other simultaneous diseases, still needing to be understood, as an attempt to increase the P-CHFrEF quality of treatment, once they are followed-up in the PHC setting. The same applies to polypharmacy, for just to treat CHF a set of 4 prognostic modifying medicines is recommended, a fifth one being necessary for symptoms relief (1,12,13).

The aim of this study was to evaluate the agreement between the most recent guidelines issued by the ESC for the treatment of P-CHFrEF, and their application in PHC, in the central region of Portugal.

This data will be presented in the respective Primary Care Health Unit, with the aim of trying to correct any errors and optimize the treatment CHFrEF.

METHODS

Study design

An observational cross-sectional randomized study in a population of 2381 patients diagnosed with CHF (K77, ICPC-2), for December the 31st, 2021 was performed.

The approval of the Ethics Committee of the Regional Health Administration of the Center (ARS Centro) was requested, which was positive (Annex I).

Participants selection

Central of Portugal eleven disseminated PHC Units: UCSP Cantanhede, USF Mondego, UCSP Soure, USF Fernando Namora, USF Anadia, UCSP Campos do Liz, USF Rainha Santa Isabel, USF Figueiró dos Vinhos, USF Pombal, USF Esgueira, USF Grão Vasco were conveniently invited in and accepted. From this population of 2381 persons diagnosed with Chronic Heart Failure (CHF) from which 453 with CHFrEF (P-CHFrEF) were retrieved, a proportional size representative sample of n=133, 95% confidence interval and 5% margin error calculated was studied. Anonymity and confidentiality in accessing the PHC Units clinical database was granted, all doctors being access-allowed to collect data that were anonymously transmitted to the investigators.

As inclusion criteria:

- PCHF followed-up in General Practice/Family Medicine appointments with a diagnosis of CHF encoded in the SClinico® software, the official clinical e.registration program;
- Patients with LVEF ≤40% documented by echocardiography;
- Patients with known pharmacological treatment documented in PEM software, the Portuguese electronic medicines prescription registry.

Data collection procedures

Initial data from the PCH Units were obtained from the informatics office of the Portuguese National Health Service central Portugal Authority, issuing a list by the National Health Service number, later transformed in each PHC Unit in an alphabetical list, that was the frame, in an inverse alphabetical order for this study. From such information, assigned general practice/family medicine internees and specialists in each PHC Unit gathered the more recent echocardiogram reports, that were studied, in consensus, by two members of the research team from which those with the P-CHFrEF ones were retrieved.

The following variables were recorded from each PCHF in SClinico® and PEM files, according to the approved protocol:

- Age and gender;
- Year of registration of the ICPC-2 K77 problem;
- Years since the last echocardiogram;
- Ongoing prognostic modifying therapy of CHFrEF: Angiotensin Conversion Enzyme-Inhibitor (ACE-I), Angiotensin 2 receptor antagonists (ARB), ARB/Neprilysin antagonists (ARNI), Beta Blocker (BB), Mineralocorticoid Antagonists (MRA), Inhibitors of SGLT2 (SGLT2-I). As in Portugal Neprilysin antagonist, Sacubitril is only prescribed in association with the ARB Valsartan, for this study those prescribed with ARNI were also considered as ARB prescribed;
- Other drugs for CHF treatment, loop diuretic, digitalis, calcium channel blockers (CCBs) and also being on non-steroidal anti-inflammatory drugs (NSAIDs), oral chronic corticotherapy, thiazide diuretic and tricyclic antidepressants was retrieved.

Statistical analysis

Data were studied using the Statistical Package for the Social Sciences (SPSS®), version 24 for Windows®. For the characterization of the sample descriptive statistical methods were used. Measures of central tendency were calculated – mean, standard deviation, median – for continuous variables.

The sample size was calculated with [https://pt.surveymonkey.com/mp/sample-size-calculator/] for a confidence interval of 95% and an 5% margin of error.

Using the Klomogorov-Smirnov test, the distribution of the numeric variables age, years with the diagnosis and years since the last echocardiogram were tested. For nominal, ordinal and numeric non-normal ones, non-parametric tests were used and a p-value <0.05 was considered significance.

RESULTS

Characteristics of participants

From a universe of n=2381 PCHF, a population of n=453 P-CHFrEF was found, a size representative sample of n=133 (5.59%), n=95 males (71.40%) was studied. Mean age was of 74.3±11.6 years, males 73.4±11.0 and females 76.6±12.9, p=0.088 and mean time since the diagnosis was of 5.8±4.8, males 5.1±4.0 and females 7.6±6.0 years, p=0.005. The mean time since the last echocardiogram was of 3.8±2.8, males 3.7±2.5 and females 4.2±3.4 years, p=0.313, according to Table 1.

Table 1. Characteristics of participants

	Sex	n	Mean	Sd	P (*)
Years with diagnosis	Female	38	7.6	6.0	0.005
	Male	95	5.1	4.0	
Years since the last echocardiogram	Female	38	4.2	3.4	0.313
	Male	93	3.7	2.5	
Age	Female	38	76.6	12.9	0.088
	Male	95	73.4	11.0	

Note: SD standard deviation; (*) Mann-Whitney U

Prescription rates for the separate drugs

Table 2 presents the prescription rates for the different classes of drugs, independently of being prognostic ones, separately considered, the most frequent ones being BB (75.2%) and Loop Diuretics (72.2%). Third and fourth most prescribed classes were SGLT2-I and MRAs, in 44.4% and 40.6%. The ARNI was prescribed in 38.3%. The ACE-I and ARB isolated were prescribed in 34.6% and 21.8% respectively. Most of the patients (94.70%) were prescribed a RAAS-I. For 4 patients, prescription of ACE-I and ARB was found and for one there was a prescription of ACE-I and ARNI simultaneously.

Table 2. Prescription rates for the separate drugs

	Loop diuretics	ACE-I	ARB	ARNI	BB	MRAs	SGLT2-I	Digitalis	CCBs	Thiazide diuretic
n	96	46	29	51	100	54	59	15	30	12
%	72.2	34.6	21.8	38.3	75.2	40.6	44.4	11.3	22.6	9.0

Table 3 presents the number of patients on a combination of 3 or more prognostic modifying medicines and less than 3 prognostic modifying therapies. In this sample n=66 (49.6%) were on 3 or more prognostic modifying drugs. The ESC Guidelines acknowledges that there are 4 groups of prognostic modifying drugs, the RAAS-I (ACEI/ARNI/ARB), Beta-blockers, MRAs and SGLT2-I. Although the ARNI incorporates an ARB (valsartan, in Portugal) in its pill presentation, in this study, we considered its use independent of the use of an ARB isolated, for statistical purposes.

For women, n=16 (42.8%) were treated with 3 or more classes of prognostic modifying drugs, and for men n=50 (52.6%), not different between genders, p=0.183. For n=67 (50.4%) patients managed with less than 3 prognostic modifying drugs.

Table 3. Number of patients managed with 3 or more / less than 3 prognostic modifying medicines by sex.

		3 or more prognostic modifying therapies	Less than 3 prognostic modifying therapies	Total
Sex	Female	16 (24.2%)	22 (32.8%)	38
	Male	50 (75.8%)	45 (67.2%)	95
Total		66 (49.6%)	67 (50.4 %)	133

Table 4 presents the prescription rates for the different classes of drugs, exclusively in the subgroup of 66 patients treated with 3 or more prognostic modifying drug classes. Of the prognostic modifying drug classes, the most prescribed ones were the BB (93.9%), followed by the MRAs and the SGLT2-I (both 74.2%). ARNI were prescribed in 63.6%. The ACE-I and ARB isolated were prescribed in 33.3% and 9.1%, respectively and RAAS-I were prescribed for 72.7%. In general, the second most prescribed class was loop Diuretics (83.3%), which are symptomatic and not prognostic medicines.

Table 4. Prescription rates in patients treated with 3 or more prognostic modifying therapies

	Loop diuretics	ACE-I	ARB	ARNI	BB	MRAs	SGLT2-I	Digitalis	CCBs	Thiazide diuretic
n	55	22	6	42	62	49	49	11	11	4
%	83.3	33.3	9.1	63.6	93.9	74.2	74.2	16.7	16.7	6.1

Combination regimes of prognostic modifying therapies

Quadruple combination regimes

According to Table 5, 28 patients (21.1%), 20 men and 8 women, were on a quadruple combination regime. The most frequent quadruple modifying prognosis association was ARNI + BB + MRA + iSGLT2, in 23 patients (17.3%), with n=19 (82.6%) of them simultaneously medicated with a loop diuretic.

Table 5. Quadruple combination regimes

	Male n (%)	Female n (%)	Total n (%)
ARNI + BB + MRA + SGLT2-I	16 (16.8)	7 (18.4)	23 (17.3)
BB + ACEI + MRA + SGLT2-I	3 (33.0)	1 (3.3)	4 (3.0)
BB + ARB + MRA + SGLT2-I	1(1.1)	0	1 (0.8)
Total	20 (21.1)	8 (21.1)	28 (21.1)
% (out of the sample)	15.0	6.0	17.3

Triple combination regimes

The triad of an RAAS-I, a BB, and an MRA is recommended as cornerstone therapy for PCHF, unless the drugs are contraindicated or not tolerated.

For n=38 patients (28.6 %), 30 men and 8 women, prognostic-modifying triple therapy regime was prescribed. Out of these 38 patients, 16 (42.1%) were on the abutment association of an RAAS-I + BB + MRA. For n=9 (56.3%) the association of valsartan with Sacubitril was prescribed and for n=7 (43.8%) the RAAS-I was an ACE-I. In 15 (93.8%) a loop diuretic was also prescribed. For other n=16 (42.1%) patients the association of either an ACE-I or an ARB + BB + SGLT2-I was present, the valsartan with Sacubitril association on 56.3%. In this group n=12 (75.0%) were also on a loop diuretic treatment. Other 6 patients on triple therapy, n=4 (3 men and 1 woman), were on a RAAS-I + SGLT2-I + MRA and two male patients were on BB + SGLT2-I + MRA. Table 6 presents the results for triple combination regimes.

The triple cornerstone therapy (RAAS-I + BB + MRA), whether associated with another prognostic modifying drug or not, was prescribed for 44 patients (33.1%) of which 28 (63.6%) were concomitantly medicated with SGLT2-I. According to the ESC guidelines, all patients undergoing this triple therapy, regardless of whether they are diabetic or not, must also be considered for treatment with SGLT2-I.

Table 6. Triple combination regimes

	Male n (%)	Female n (%)	Loop Diuretic
RAAS-I + BB + MRA	11 (36.7)	5 (62.5)	15 (48.4)
RAAS-I + BB + SGLT2-I	14 (46.7)	2 (25.0)	12 (38.7)
RAAS-I + SGLT2-I + MRA	3 (10)	1 (12.5)	3 (9.7)
BB + SGLT2-I + MRA	2 (6.7)	0	1 (3.2)
N	30	8	31
% (out of the total)	22.6	6.0	23.3

Double combination and monotherapy and other regimes.

Double prognostic-modifying therapy was verified in 47 P-CHFrEF (35.3%), 34 men and 13 women. Out of these, 33 (71.7%) were on a RAAS-I + BB. The second most frequent double association was a RAAS-I + SGLT2-I in 9 (19.1%) patients (8 men and 1 woman). The combinations of a RAAS-I + MRA and BB + MRA were found in 3 (6.4%) and 2 (4.3%) patients, respectively. Also, out of these 47 patients, 32 (68.1%) were simultaneously medicated with a loop diuretic. For 1 patient a simultaneous prescription of ACE-I and ARB was found.

For 17 P-CHFrEF (12.7%), 10 men and 7 women, only one prognostic modifying medicine was prescribed, 12 (70.6%) P-CHFrEF medicated with a RAAS-I: 5 (29.4%) with an ACE-I, 4 (33.3%) with valsartan+sacubitril and 3 (25.0%) with ARB. The second most frequent drug in monotherapy was the BB for 4 (23.5%). Finally, only 1 (5.9%) P-CHFrEF was medicated with iSGLT2 in monotherapy. In this group of P-CHFrEF, on only one prognostic modifying medicine, n=8 (47.1%) were simultaneously medicated with a loop diuretic (47.1%).

For 3 (2.2%) P-CHFrEF no treatment with prognostic modifying drugs was found. For 96 (72.2%) P-CHFrEF loop diuretic was prescribed, 12 (9.2%) were prescribed with thiazide diuretics, 8 of which (66.7%) under suboptimal therapy.

Digitalis were prescribed in 15 P-CHFrEF (11.3%), out of which 11 (73.3%) were simultaneously medicated with the optimized CHFrEF therapy. The use of CCB was verified in 30 P-CHFrEF (22.6%), with 19 (63.3%) on a suboptimal CHFrEF therapy.

In 18 P-CHFrEF (13.5%) a NSAID medicine was prescribed, 9 (50%) simultaneously on 3 or more prognostic modifying drugs. In 3 P-CHFrEF (2.3%) corticosteroid therapy was prescribed, 2 of them under suboptimal CHFrEF therapy.

DISCUSSION

The main objective of this study was to analyze the management of PCHF and prescription of CHF prognostic modifying medicines and to assess the agreement between therapy currently performed in primary care centers and current ESC guidelines for the treatment of CHFrEF, in a representative random study of patients from 11 invited primary health care units in central Portugal.

According to the most recent ESC guidelines for the treatment of CHFrEF, all patients should start their medicine's therapy with the combination of the 4 groups of prognostic modifying medicines, a RAAS-I (ACE-I/ARNI preferably or an ARB on patients unable to tolerate an ACE-I or ARNI), a Beta-blocker, a MRA and an SGLT2-I (12,13). Out of the 133 patients, 66 (49.6%) were being medicated with 3 or more classes of prognostic modifying therapies and the optimized medical quadruple therapy was verified in 28 patients (21.1%).

The RAAS-I + BB duo, whether alone or associated with other therapies, was present in 93 patients (69.9%). This result, seeming relatively low, contrasts with other studies (3,4 ,7,8,10) in which a much lower use of the combination of RAAS blockade and BB was found. Also, the individual prescription rates for these two drug classes stood out, as 91.0% were prescribed a RAAS-I and 75.2% with BB, contrasting with previous studies with lower prescription rates of RAAS-I (3 4,8,10) and BB (3 4,8,10). A possible explanation for the high use of RAAS-I as well as BB might be that these agents were present in earlier recommendations for the treatment of CHF and also because they were originally initiated to treat hypertension and/or ischemic heart disease and not CHF.

The triad of RAAS-I, beta-blocker, and MRA is recommended as cornerstone therapy for these patients, unless the medicines are contraindicated or not tolerated (6). This triple cornerstone therapy was prescribed for 33.1%, from which 63.6% were concomitantly associated with SGLT2-I. According to the ESC guidelines as well as DAPA-HF(14) study in 2019 and EMPEROR-reduced (15) study in 2020, all patients undergoing this triple therapy, regardless of whether they are diabetic or not, should be considered for treatment with SGLT2-I, which was only prescribed in 63.6% of patients in this subgroup. Out of the 38 patients (28.6%) undergoing prognostic-modifying triple therapy, only 16 (42.1%) were being medicated with this association. These patients, despite not being completely in accordance with the ESC guidelines since they do not have a SGLT2-I associated (6), have the main triad. There are still another 16 patients being medicated with the combination of RAAS-I + BB +

ISGLT2, which despite complying with triple therapy, does not fulfill the cornerstone triad requirement.

Despite the individual prescription rates of 3 or more prognostic modifying medicines classes in this study being of 49.6%, higher than other previous studies (3,4,7,10,13,17), such findings indicate non-complete accordance with the current ESC guidelines, as only 21.1% of patients were treated with the quadruple optimal treatment.

So, it is important to try to understand why PCHF are still under-treated or are on less adequate combinations.

As an explanation for this General Practice/Family Doctors (GP/FD) are ever more managing frail, multimorbid, polymedicated old patients (2,13,18). Multimorbidity has been shown to have a significant impact on how recommended pharmacological therapies are prescribed for GP/FDs must take medicines interactions and competing therapeutic requirements into account (2,18,19). Many GP/FD can also be reluctant about starting new recommended medicines in elderly because of fear that patients will not be able to tolerate them, suffer adverse drug reactions or because of price concerns (17,20,21). Clinical therapeutic inertia is a problem to be dealt with from CHF diagnostic (1).

Considering the sample's mean age**,** could be argued that the proposed optimal quadruple therapy that is used in controlled studies (13,15) is not always applicable for elderly, frail patients with multimorbidity and with risk of polypharmacy consequences, with pharmacodynamics and pharmacokinetic interactions (2,17,18).

One very common reason for the non-compliance of therapy recommendations is clinical inertia, as many physicians may believe that stability of symptoms means stability of the underlying disease process. However, the underlying disease continues to progress even if symptoms are alleviated. Loop diuretics are the medicines class for symptomatic control. So less symptomatic patients could lead to clinical inertia and therefore suboptimal treatment even with prognostic medicines. This was not verified in the present study, as 83.3% of the patients on 3 or more prognostic modifying medicines were simultaneously medicated with a loop diuretic, in contrast to the 61.2% on less than 3 prognostic modifying medicines.

Two relatively recent therapeutic classes of medicines were recommended for treatment of PCHF, particularly P-CHFrEF, ARNI and SGLT2-I. The present results show an apparent non-inertia once the prescription rates of SGLT2-I (44.4%) and ARNI (38.3%) are

higher than some classes recommended since earlier ESC guidelines: ACE-I (33.3%), ARB (21.8%) and MRAs (40.6%).

A significant limitation to the widespread adoption of the recommended therapeutic strategy, is the lack of any existing framework allowing PHC physicians to describe the adequacy of the implemented treatment. In clinical practice, practitioners commonly state that their treatment plan is guideline-directed medical therapy (16). Actually, there is no implemented framework to describe the degree to which a patient's medical regimen adheres to, or deviates from, the recommendations presented by the ESC guidelines.

Other important limitations to the current situation can be the less specific recommendations in earlier guidelines, poor PCHF follow-up and uncertainty of the diagnosis by the patient himself.

The comparison of prescription frequency between ARNI (38.0%) and iSGLT2 (44.4%) is also interesting, since these two drugs are the latest additions to the CHFrEF prognostic modifying treatment regimen. The prescription rate for the iSGLT2 being already higher than the prescription rate for the ARNI, even though the iSGLT2 approval is more recent, is probably justified by the other therapeutic indications and easy handling. Also, the proportion of prescription rates between the three different medicines in the RAAS-I is interesting since the ARNI, despite being the most recent addition to this class is already more prescribed than ACE-I and ARB isolated. This result is in line with other studies (3,22) that demonstrate a rapid increase in ARNI utilization, due to extensive evidence from clinical trials and accumulating knowledge from real-world clinical practice (22). In the PCHF context, this result is a clear sign that, despite major improvements in the therapeutic management there is still space for amelioration.

To address these liabilities a simple informatics approach to PHC physicians could be a pop-up asking about 1- whether PCHF was receiving each of the recommended prognostic modifying medicines; 2- whether PCHF was on target doses of each of these medicines; and 3- whether PHCF had been tried on the medicines/optimal doses and could not be tolerated, despite efforts at rechallenge or adjustment of other medications; 4-wether the PCHF had been checked for literacy about CHF(23), medicine's adherence (24) and pharmacokinetic or pharmacodynamics medicine's interactions. Such framework could lead the PHC clinician to comprehensibly and optimally treat the PCHF.

The presence of NSAIDs prescription in 18 P-CHFrEF (13.5%) is somehow worrisome, representing suboptimization of CHF therapy, revealing pain as a, or the problem for old age patients.

According to the guidelines, the monitoring of P-CHFrEF implies an annual echocardiogram for revaluation. There is the issue of patients who clinically no longer benefit from carrying out this surveillance. On the basis of this uncertainty, in this study we considered this factor could be circumvented by considering only the ≤80y population. Therefore, considering the 87 patients aged ≤80y, the mean time since the last echocardiogram was 3.48 years. Comparing this result with the mean time for the whole group of patients which includes the patients aged >80 years, 4.21 years for women and 3.67 years for men, one perceives that for younger patients, the reevaluation echocardiogram, while still far from indicated, is carried out more according to the recommended timings (25,26)

The CHFrEF patients' literacy must be studied and used to individually inform each patient. In fact, knowledge is crucial for adequate pharmacologic and non-pharmacologic treatment performing Patient Centered Medicine (27,28)

CONCLUSION

Underutilization of the most recent evidence-based medicine treatments to reduce morbidity and mortality in PCHF, particularly the P-CHFrEF in the PHC setting, regarding prescription of combination regimes according to recommended ESC guidelines was found for 50.4%. Longer than recommended intervals for echocardiogram were also found, 3.8±2.8.

More information for PHC doctors and PCHF is needed for better results.

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To my family, who have always fomented my interest in Medicine and new academic achievements, but above all for always being present and celebrating each victory at my side, with pride and tenderness.

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ATTACHMENTS

Attachment I – Authorization from the Center's ARS Ethics Committee

GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

ARSC ADMINISTRAÇÃO REGIONAL DE SAÚDE DO CENTRO, I.P.

COMISSÃO DE ÉTICA PARA A SAÚDE

PARECER FINAL:	DESPACHO:
FAVORÁVEL	Homologado o parecer favorável 28-2022

Conselho Diretivo
da A.R.S. do Centro, I.P.

ASSUNTO: **Título:** "Medicação da insuficiência cardíaca nos Cuidados de Saúde Primários da região centro de Portugal: um estudo observacional em 2022", **67/2022**
Investigador: João Domingues Vaz (MIM-FMUC; co-autores: Luís Santiago e Raúl Garcia

Drª Rosa Reis Marques
Presidente,

Dr. Mário Ruivo
Vogal,

Dr. Fernando Cravo
Vogal

Pretende-se avaliar a concordância entre as diretrizes mais recentes emitidas pela ESC para o tratamento da Insuficiência Cardíaca com Fração de Ejeção reduzida (ICFEr) e a sua aplicação nos CSP, na região Centro de Portugal. Estes dados serão apresentados nas respetivas unidades funcionais, com o objetivo de tentar corrigir eventuais erros e otimizar o tratamento da ICFEr. Serão estudados os doentes com diagnóstico de IC, a partir dos quais se obterá aqueles com ICFEr. Com base nesta amostra, estudar-se-á a terapêutica instituída para esta patologia. O trabalho vai realizar-se em dois braços a decorrer simultaneamente: 1 – Dados epidemiológicos - a solicitar à ARS Centro - dos indivíduos que, a 31 de dezembro de 2021, estavam codificados com IC (K77, ICPC-2). 2 – Solicitar a colaboração de médicos, preferencialmente internos de Medicina Geral e Familiar de várias unidades funcionais da Administração Regional de Saúde do Centro, na colheita de dados sobre o tratamento dos doentes com ICFEr. Após obtenção do número de diagnósticos de ICFEr em cada unidade, calcular-se-á o tamanho da amostra e esta será proporcionalmente distribuída pelas unidades participantes, salvaguardando o anonimato e sigilo no acesso à base de dados. Os dados de cada unidade serão colhidos por médicos de cada unidade e que têm acesso a tal informação na PEM. A informação anonimizada será fornecida aos investigadores que depois de realizarem o trabalho de análise fornecerão os resultados às Unidades para que estas possam estar informadas acerca da conformidade e simultaneamente possam desencadear as necessárias medidas corretivas.

Os autores referem que o consentimento informado não se aplica porque serão estudados dados de processo obtidos em sigilo, anonimato e confidencialidade.

O Relator e Presidente da CES da ARS do Centro,

Ressalva: A CE-ARSC enfatiza que a aprovação de um estudo não significa que venha a ter qualquer responsabilidade por danos ou outros atos ilícitos que possam vir a ser praticados no âmbito do mesmo. As opiniões apresentadas nas publicações, relatórios ao governo ou outros resultados desta investigação são da responsabilidade exclusiva dos investigadores.