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Particularities of pharmacotherapy regimens in overweight and obese patients with heart failure and atrial fibrillation

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Abstract. Introduction. The classic treatment of heart failure comprises life style modification, pharmacological and non-pharmacological treatment in order to reduce/stop the progression of cardiac remodeling, improve symptoms and decrease the number of hospitalizations and associated mortality. In the current study we aimed to evaluate the treatment prescribed for obese patients with heart failure and atrial fibrillation in a Romanian Hospital. Material and methods. We conducted an analytical transversal study 130 consecutive overweight and obese patients, admitted to the Clinical Rehabilitation Hospital, Cluj-Napoca. The mean age was 70.39 ± 8.98 years, 55.4% of them were men. 46.2% patients presented with persistent or permanent atrial fibrillation. Heart failure was defined according to the recommendations of the guidelines for the diagnosis and treatment of acute and chronic heart failure published by the European Society of Cardiology in 2016. The patients were divided into 3 groups depending on the left ventricular ejection fraction (EF): preserved (≥50%) - 46.9%, slightly reduced (40-49%) - 28.46% and low (<40%) - 24.61%. All patients were assessed clinically, biochemically, echocardiographically and from the point of view of the initiated treatment. NT-pro-BNP was measured in all patients, values higher than 125 pg/ml being considered pathological. The intra-hospital therapeutic strategy was analyzed for all patients, taking into consideration the associated comorbidities or the immediate adverse effects. Statistics were performed using SPSS 16.0 for Windows. Results. No statistically significant differences were observed between the patients with or without atrial fibrillation, except for left atrium size, which was obviously larger in patients with atrial fibrillation. The majority of the patients included in the study received treatment recommended by current guidelines. Obviously, anticoagulant drugs were administered in a higher proportion to patients with atrial fibrillation. ACEIs were indicated in the highest proportion for patients with preserved ejection fraction (p=0.034), ARBs and nitrates for those with slightly reduced ejection fraction (p=0.0054 and 0.0001, respectively). The most frequently used antiarrhythmic drug was amiodarone, administered to 23.84% of patients with heart failure in general, and 51.6% of those with atrial fibrillation. Regarding the atrial fibrillation ablation procedure, this was performed in 6 patients (4.6%). In conclusion, the treatment of obese patients with atrial fibrillation, despite having certain particularities, was similar with that prescribed in patients without atrial fibrillation, except for anticoagulant and antiarrhythmic medication.

Key Words: heart failure, obesity, atrial fibrillation, heart failure treatment

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Introduction

Although, there is a well-known association between obesity and heart failure development, patients with established heart failure and overweight or class I obesity have better outcomes in comparison with their lean counterparts – the "obesity paradox" phenomenon (Horwich et al 2018). More severe obesity is generally associated with poor prognosis. Moreover, commonly obese patients develop heart failure with preserved ejection fraction (HFpEF). To date, there is no available therapy which increases survival in patients with HFpEF (Montero et al 2017). Further studies are needed in order to characterize more homogeneous subgroups of patients suffering from HFpEF in order to move to a more personalized approach.

On the other hand, the treatment of heart failure with reduced ejection fraction (HFrEF) is well established in current guidelines for the diagnosis and treatment of heart failure. The classic treatment of heart failure comprises life style modification, pharmacological and non-pharmacological treatment in order to reduce/stop the progression of cardiac remodeling and heart dysfunction, to improve symptoms and decrease the number of hospitalizations and associated mortality. Unfortunately, despite all these remarkable advances in the treatment of heart failure with reduced ejection fraction, it remains a continuously growing public health issue. Besides, heart failure with preserved ejection fraction (HFpEF) and mid-ranged ejection fraction (HFmrEF) have an extremely heterogeneous etiology, pathophysiology and phenotype expression, their treatment being challenging and complex. Patients with cardiovascular or non-cardiovascular comorbidities usually develop HFpEF or HFmrEF (Ponikowski et al 2016). Moreover, studies have shown that none of the class I anti-neuroendocrine therapeutic strategies for HFrEF has so far proven its effectiveness in improving the prognosis of patients with HFpEF and HFmrEF, respectively (Ponikowski et al 2016; Montero & Flammer 2017). Progress has been much less pronounced in the treatment of HFpEF and HFmrEF. Patients with heart failure have various associated arrhythmias, such as atrial fibrillation, the most common sustained cardiac arrhythmia, which involves initiation of a more complex personalized pharmacotherapy regimen.

The main classes of drugs indicated in current guidelines are angiotensin converting enzyme inhibitors/angiotensin AT1 receptor blockers (ACEIs/ARBs), along with beta-blockers (a class IA indication in all patients with an ejection fraction EF < 40%), aldosterone antagonists (a class IA indication in symptomatic patients despite the mentioned medication with an EF < 35%), ivabradine, digoxin (Ponikowski et al 2016). Large trials have shown that patients with HFpEF and HFmrEF more rarely benefit from treatment with ACEIs/ARBs, diuretics, beta-blockers, aldosterone antagonists compared to those with HFrEF (Ponikowski et al 2016). The presence of atrial fibrillation involves supplementation of treatment with various antiarrhythmics and anticoagulants. In this context, in the current study we aimed to evaluate the treatment prescribed for obese patients with heart failure and atrial fibrillation, especially in patients with HFpEF and HFmrEF, where the current guidelines acknowledge a lack in evidence (Ponikowski et al 2016) and to highlight several pharmacological treatment particularities. To date, personalization of pharmacotherapies in heart failure in this subgroup of patients is still poorly defined.

Materials and methods

The study included 130 overweight and obese patients (body mass index ≥ 25 kg/m2), with a mean age of 70.39 ± 8.98 years, 55.4% men, admitted to the Clinical Rehabilitation Hospital, Cluj-Napoca. 46.2% of patients were diagnosed with persistent or permanent atrial fibrillation. Heart failure was defined according to the recommendations of the guidelines for the diagnosis and treatment of acute and chronic heart failure published by the European Society of Cardiology in 2016 (Ponikowski et al 2016). All patients were assessed clinically, biochemically, echocardiographically and from the point of view of the initiated treatment. NT-pro-BNP assays were performed in all patients, upon initial assessment and values above 125 pg/ml were considered pathological (Ponikowski et al 2016). The intra-hospital course, procedures and medical therapy were analyzed for all patients, taking into consideration the associated comorbidities or the immediate adverse effects. Statistics were performed using SPSS 16.0 for Windows. Analysis of the differences between qualitative variables was carried out using the $\chi 2$ test. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous numerical variables. Categorical data were summarized with absolute numbers (No) and percentages and numeric data as means and standard deviations (SD). Values of $p<0.05$ were considered statistically significant.

The study was approved by the Hospital Ethics Committee and the selected patients were informed about the study protocol and gave their signed informed consent.

Results

The baseline demographic and clinical characteristics of the patients are summarized in Table 1.

Atrial fibrillation (AF) was found in 60 patients (46.2%), of which 25 were women (41.6%). Of the 60 patients, 55% (33 patients) had atrial fibrillation with rapid atrioventricular conduction as a triggering factor of worsening heart failure. No statistically significant differences were observed between patients with and without AF, except for left atrium (LA) dilatation, which was obviously more frequently found in patients with AF. NT-pro-BNP values were significantly higher compared to the cut-off value of 125 pg/ml, but not significantly different between patients with and without AF.

The majority of the patients included in the study received treatment recommended by current guidelines (Ponikowski et al 2016). Thus, the main classes of drugs recommended at discharge were ACEIs/sartans (in case of ACEI intolerance or irritating cough) along with beta-blockers, aldosterone antagonists, ivabradine, digoxin – Table 2. It can be seen that there were no significant differences between patients with and without atrial fibrillation, except for long-acting nitrates, administered in a higher proportion to patients without atrial fibrillation, digoxin indicated more frequently in patients with heart failure and AF, and anticoagulants, obviously present in the therapeutic plan of all patients with this arrhythmia.

The patients were divided into 3 groups depending on the left ventricular ejection fraction (EF): preserved (≥50%) - 46.9%, slightly reduced (40-49%) - 28.46% and low (<40%) - 24.61%. Table 3 synthesizes the treatment of patients depending on the left ventricular ejection fraction (LVEF) value.

ACEIs were indicated in the highest proportion for patients with preserved ejection fraction (p=0.034), ARBs and long-acting nitrates for those with slightly reduced ejection fraction (p=0.0054 and 0.0001, respectively). The sacubitril/valsartan combination was prescribed only for a small number of patients with heart failure with reduced ejection fraction. Also, therapy with MRA in addition to standard heart failure therapy mentioned above recommended mostly in patients with heart failure with severe reduced ejection fraction and also in patients with HFmrEF. Also, digoxin was prescribed especially in patients with HfrEF as a discharge medication. For the rest of the medication, there were no significant differences depending on the LVEF.

The most frequently used antiarrhythmic drug was amiodarone, administered to 23.84% of patients with heart failure in general, and 51.6% of those with atrial fibrillation in those patients with persistent AF and in few cases for rate control. The most frequently recommended bradycardic therapy (also having antiarrhythmic properties) was represented by beta-blockers -96.9% of patients in general (97.6% of those with atrial fibrillation), and digoxin was administered as long-duration oral therapy only in patients with atrial fibrillation with rapid atrioventricular conduction and HFrEF or HFmrEF. For prevention of thromboembolic events, anticoagulant treatment was prescribed to all patients with atrial fibrillation: acenocumarol - 30%, direct oral anticoagulants (DOAC) - 70%. From Table 2 it can be seen that anticoagulant treatment was also recommended for 17.1% of patients without atrial fibrillation who were in sinus rhythm at the time of their inclusion in the study.

Regarding the atrial fibrillation ablation procedure, this was performed in 6 patients, representing 4.6%.

Discussions

Obese patients with heart failure most frequently have preserved ejection fraction. They have diagnostic, therapeutic and prognostic particularities of heart failure that can make difficult both the diagnosis and the treatment of heart failure, especially if atrial fibrillation (AF) is present. The latter represents the most frequent cardiac arrhythmia in patients with heart

Table 1. Baseline demographic and clinical features of patients with worsening heart failure with or without AF.

		All patients	With atrial fibrillation	Without atrial fibrillation	P value
		130	60 (46.2)	70 (53.8)	
Age Mean ± SD		70.39±8.98	70.95±9.59	69.91±8.46	NS
Sex No (%)	Women	58 (44.6)	27 (45)	31 (44.28)	NS
	Men	72 (55.4)	33 (55)	39 (55.71)	
Etiology of heart failure No (%)	Due to chronic lung disease	12 (9.2)	5 (8.33)	7 (10)	NS
	Ischaemic heart disease	65 (50)	30 (50)	35 (50)	
	Heart valve disease	13 (10)	6 (10)	7 (10)	
	Other cardio-vascular conditions (arrhythmia, hypertension, etc)	40 (30.8)	19 (31.66)	21 (30)	
NYHA class No (%)	II	38 (29.2)	17 (28.33)	21 (30)	NS
	II/III	6 (4.6)	1 (1.66)	5 (7.14)	
	III	66 (50.8)	31 (51.66)	35 (50)	
	III/IV	5 (3.8)	3 (5)	2 (2.87)	
	IV	15 (11.5)	8 (13.33)	7 (10)	
NT-pro-BNP Mean±SD (median) pg/ml		2684.53±3636.55 (1329.5)	3022.38±4259.90 (1833)	2395.63±3006.14 (1233)	NS
Smoking No (%)		48 (36.9)	20 (33.33)	28 (40)	
Total cholesterol –mg/ml Mean±SD		167.90±46.16	174.06±49.73	162.61±42.51	NS
Creatinine mg/ml Mean±SD		1.10±0.39	1.12±0.37	1.08±0.41	NS
Creatinine clearance ml/ min Mean±SD		90.07±34.06	90.14±39.69	90.02±28.66	NS
DM No (%)		45 (34.6)	17 (28.3)	28 (40)	NS
Peptic ulcer No (%)		48 (36.9)	24 (40)	24 (34.28)	NS
BMI Mean±SD		34.65±4.56	35.16±4.75	34.20±4.37	NS
Obesity No (%)	Grade I obesity	62 (47.7)	29 (48.3)	33 (47.1)	NS
	Grade II obesity	35 (26.9)	15 (25)	20 (28.6)	
	Grade III obesity	17 (13.1)	10 (16.7)	7 (10)	
	Overweight	16 (12.3)	6 (10)	10 (14.3)	
HTN No (%)		94 (72.3)	45 (75)	49 (70)	NS
Charlson Comorbidity Score Mean±SD		5 (4.63±1.43)	5 (4.88±1.64)	4 (4.42±1.18)	NS
LA antero-posterior diameter (mm) Mean±SD		47.06±9.31	50.15±9.17	44.42±8.65	0.000
LA area cm² Mean±SD		25 (27.26±8.08)	30 (30.25±7.85)	22.1 (24.69±7.40)	< 0.0001
Ejection fraction No (%)	40-49	37 (28.5)	18 (30)	19 (27.1)	NS
	<40	32 (24.6)	12 (20)	20 (28.6)	
	≥50	61 (46.9)	30 (50)	31 (44.3)	

Table 2. Treatment of patients depending on the presence of atrial fibrillation

		All patients	With atrial fibrillation	Without atrial fibrillation	p
ACEIs		75 (57.7)	33 (55)	42 (60)	NS
	Fosinopril	3 (4)	2 (6.1)	1 (2.4)	
	Lisinopril	1 (1.3)	0 (0)	1 (2.4)	
	Perindopril	50 (66.7)	24 (72.7)	26 (61.9)	NS
	Ramipril	19 (25.3)	6 (18.2)	13 (31)	
	Trandolapril	1 (1.3)	1 (3)	0 (0)	
	Zofenopril	1 (1.3)	0 (0)	1 (2.4)	
Sartans		49 (37.7)	26 (43.3)	23 (32.9)	NS
	Candesartan	17 (34.7)	8 (30.8)	9 (39.1)	0.057
	Irbesartan	2 (4.1)	2 (7.7)	-	
	Losartan	5 (10.2)	5 (19.2)	-	
	Olmesartan	5 (10.2)	4 (15.4)	1 (4.3)	
	Telmisartan	10 (20.4)	4 (15.4)	6 (26.1)	
	Valsartan	10 (20.4)	3 (11.5)	7 (30.4)	
Sacubitril/valsartan		4 (3.1)	0	4 (5.7)	NS
Beta-blockers		126 (96.9)	58 (96.7)	68 (97.1)	NS
	Bisoprolol	32 (25.4)	17 (29.3)	15 (22.1)	NS
	Carvedilol	11 (8.7)	7 (12.1)	4 (5.9)	
	Metoprolol succinate	35 (27.8)	17 (29.3)	18 (26.5)	
	Metoprolol tartrate	26 (20.6)	8 (13.8)	18 (26.5)	
	Nebivolol	22 (17.5)	9 (15.5)	13 (19.1)	
If channel inhibitors - ivabradine		6 (4.6)			
Nitrates		26 (20)	7 (11.7)	19 (27.1)	0.047
Calcium channel blockers		6 (4.6)	5 (8.3)	1 (1.4)	NS
Digoxin		39 (30%)	36 (27%)	3 (2.3%)	<0.0001
Mineralocorticoid receptor antagonists (MRAs)		78 (61.9%)	56 (43%)	22 (57%)	NS
Loop diuretics		110 (84.6%)	60 (46.2)	50 (38.4)	NS
Antiarrhythmics		41 (31.5)	41 (31.5)	-	
	Amiodarone	31 (23.84)	31 (51.6)	-	
	Flecainide	4 (3.07)	4 (6.66-)	-	
	Propafenone	5 (12.2)	5 (12.2)	-	
Anticoagulants		72 (55.4)	60 (100)	12 (17.1)	< 0.0001
	Acenocumarol	19 (26.4)	18 (30)	1 (8.3)	
	Apixaban	22 (30.6)	17 (28.3)	5 (41.7)	
	Dabigatran	15 (20.8)	12 (20)	3 (25)	
	Rivaroxaban	16 (22.2)	13 (21.7)	3 (25)	

Table 3. Treatment of patients depending on the ejection fraction

	Global	LVEF			P value
		40-49%	<40%	≥50%	
Total No of patients		37	32	61	
ACEIs	75 (57.7)	15 (40.5)	19 (59.4)	41 (67.2)	0.034
Sartans	49 (37.7)	22 (59.5)	9 (28.1)	18 (29.5)	0.005
Sacubitril/valsartan	4 (3.1)	0 (0)	4 (12.5)	0 (0)	0.002
Beta-blockers	126 (96.9)	35 (94.6)	31 (96.9)	60 (98.4)	NS
Ivabradine	6 (4.6)	2 (5.4)	2 (6.2)	2 (3.3)	NS
Long-acting nitrates	26 (20)	0 (0)	23 (71.9)	3 (4.9)	**P < 0.0001**
Calcium channel blockers	6 (4.6)	3 (8.1)	1 (3.1)	2 (3.3)	NS
Loop diuretics	110 (84.6)	35 (94.5)	32 (100)	43 (70.49)	NS
Anti-aldosterone agents (MRAs)	78 (61.9)	33 (89.1)	32 (100)	13 (21.3)	P<0.001 between patients with LVEF>40% and those with LVEF <40%
Digoxin	39 (30)	13 (35)	26 (81)	0 (0)	**P<0.001**
Antiarrhythmics	41 (31.5)	10 (27)	11 (34.6)	20 (32.8)	NS
Anticoagulants	72 (55.4)	20 (54.1)	19 (59.4)	33 (54.1)	NS

failure, regardless of the ejection fraction value (Ponikowski et al 2016). Obesity is an independent risk factor for the development of atrial fibrillation, a risk that is directly proportional to the BMI value (Wang et al 2015; Kirchhof et al 2016). But, the same phenomenon- "the obesity paradox" has been described in AF patients, too. Atrial dilation and dysfunction secondary to cardiomyopathy induced by obesity can be largely responsible for the development, recurrence and progression of atrial fibrillation. This atrial remodeling is frequently accompanied by electrophysiological remodeling (Pathak et al 2015). Other mechanisms involved in the triggering of this arrhythmia are adipose tissue deposition on the posterior wall of the left atrium, which is independently associated with the development of atrial fibrillation, intramyocardial fibrosis that favors the appearance of re-entry circuits, as well as paracrine mechanisms, various adipo-fibrokines having pro-arrhythmogenic effects (Pathak et al 2015; Zheng et al 2014).

Weight management of obese HF patients remains controversial, since robust data concerning the beneficial or detrimental implications of cardiac metabolic remodelling are lacking. This recently described phenomenon in heart failure is due to diminished cardiomyocyte fatty acid oxidation, but the glucose uptake and glycolysis are increased (De Rosa et al 2018). The current guideline (Ponikowski et al 2016) recommends weight loss only in patients with class II and III obesity (BMI 35-45 kg/m2) in order to improve symptoms and exercise capacity. Overweight individuals and those with class I obesity should be included in cardiovascular rehabilitation programs, focused on aerobic exercise training and maintenance of body weight, improving other cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia. The other lifestyle recommendations in this group of patients remain the classic ones (Ponikowski et al 2016).

Pharmacological treatment of heart failure in obese patients with atrial fibrillation should include all classes of drugs indicated by guidelines, to which anticoagulants and antiarrhythmic medication should be added. In our study, the recommended medication was in accordance with the recommendations of guidelines (Ponikowski et al 2016; Yancy et al 2017), and there were no statistically significant differences between the heart failure specific medication of patients with and without atrial fibrillation. Once again, it is important to administer ACEIs/ARBs and anti-aldosterone agents, respectively, in the presence of atrial fibrillation, because these have important effects in preventing atrial remodeling (Kirchhof et al 2016; January et al 2014; Hsieh et al 2016; Chaugai et al 2016; Khatib et al 2013). Atrial fibrillation guidelines make recommendations in this regard (Kirchhof et al 2016; January et al 2014). At the same time, due to the increased production of components of the renin-angiotensin-aldosterone system in the adipose tissue of obese patients, the treatment of heart failure should be individualized in this category of patients. ACEIs lead to a considerable decrease of serum angiotensin II, but their effects on angiotensin II produced in tissues depend on lipophilic properties (Shah et al 2005). Studies show that 45% of heart failure patients on chronic treatment with ACEIs maintain high serum angiotensin II concentrations (van de Wal et al 2016). This could be explained by the poor inhibition of angiotensin converting enzyme produced in tissues. Antagonizing the effects of angiotensin II by using AT1 receptors blockers, which seem to be well expressed in adipose tissue might be superior to ACEIs in the treatment of chronic heart failure in patients with obesity (Yagawa et al 2017).

There are studies which focused on different heart failure subgroups who are more likely to experience the greatest MRA benefit. Trials such as EMPHASIS-HF have demonstrated that eplerenone treatment leads to a significant decrease in the morbidity and mortality of these patients, both those with heart failure with reduced ejection fraction and those with preserved ejection fraction (Girerd et al 2015). In the current study, 62% of the patients received treatment with aldosterone antagonists. The TOPCAT trial, where spironolactone was used, did not

demonstrate a significant decrease in the mortality of cardiovascular cause among patients with heart failure with preserved ejection fraction (Pitt et al 2014). However, it should not be forgotten that leptin, secreted in a high proportion in the presence of obesity, stimulates renal sodium reabsorption through a mechanism mediated by glucocorticoid receptors (Packer et al 2018). Thus, a higher efficacy compared to eplerenone can be attributed to spironolactone, which also antagonizes glucocorticoid receptors (Packer et al 2018).

Obviously, all patients with atrial fibrillation received anticoagulant therapy for the prevention of thromboembolic events. It can be seen that among anticoagulants, direct acting non-vitamin K antagonist oral anticoagulants- DOACs (apixaban, followed by rivaroxaban and dabigatran) predominated in the therapeutic plan. The fact that there was also a small proportion of patients without atrial fibrillation who had anticoagulants in their therapeutic plan can be explained as follows: either they belonged to the category of patients with a history of fibrillation who were currently in sinus rhythm, or they had other anticoagulant indications, such as prevention of pulmonary or venous thromboembolism. But, a major concern regarding obese AF patients remains the risk of underexposure to DOAC, leading to a lower antithrombotic effect. The fixed dose DOACs regimens, without dose adjustment for BMI could be associated with a lack of effectiveness or safety (Tittl et al 2018). For example, the RE-LY trial showed that Dabigatran 150 mg has a better effect in patients with lower body weight (BMI<28 kg/m2) than in those with a body weight > 100 kg (Shulman, et al 2009). On the other hand, other important trials (ARISTOTLE, ROCKET-AF) showed a better outcome, with a lower stroke risk in obese patients in comparison with their lean counterparts - "obesity paradox" (Sandhu et al 2016; Balla et al 2017). There are studies showing that obesity affects the quality of anticoagulation in terms of time in therapeutic range (TTR) in those patients with vitamin K antagonists (VKA). In our study, only 30% of patients were treated with VKA (Tittl et al 2018).

Of the antiarrhythmics recommended by atrial fibrillation guidelines (4,8), the most frequently prescribed was amiodarone, followed by propafenone and flecainide (the last one is not available in Romania).

Conclusion

In this study the treatment of obese heart failure patients with atrial fibrillation, was identical to that of patients without atrial fibrillation, except for digoxin, anticoagulant and antiarrhythmic medication.

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