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Original article

Safety and Tolerability of Neurohormonal Antagonism in Cardiac Amyloidosis

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ABSTRACT

Background: Drugs for neurohormonal antagonism are usually denied to patients with cardiac amyloidosis (CA) because of safety concerns.
Methods: Patients diagnosed with CA at a tertiary referral centre from 2009 to 2019 were enrolled. In the absence of contraindications, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARB), and mineralocorticoid receptor antagonists (MRA) were started or up-titrated.
Results: 99 patients were evaluated (72% men, age 80 years [72,83], 33% light-chain and 67% transthyretin amyloidosis); 56% were started on or underwent up-titration of a beta-blocker, 25% of ACEi/ARB, and 39% of MRA; beta-blockers were then prescribed to 87% of patients, ACEi/ARB to 75%, and MRA to 63%, with median bisoprolol, ramipril, valsartan, and spironolactone daily equivalent doses of 2.5 mg, 5 mg, 80 mg, and 25 mg, respectively. Patients starting or starting/up-titrating a beta-blocker did not show a higher frequency of hypotension, fatigue, syncope, symptomatic bradycardia, need for pacemaker implantation, or HF hospitalization. Lower stroke volume and cardiac output (CO) predicted HF hospitalization regardless of amyloidosis type; lower left ventricular ejection fraction predicted hypotension, and lower CO and diastolic blood pressure predicted syncope. Patients who had an ACEi/ARB or MRA being started or up-titrated did not experience more adverse events than other patients.
Conclusions: ACEi/ARB and MRA can be safely used in CA, provided that no contraindications are present, treatment is started at a low dose and slowly up-titrated, and patients are monitored quite closely. Beta-blocker therapy is less tolerated in patients with AL amyloidosis and/or worse haemodynamic function.

1. Introduction

Amyloidosis is a systemic disease characterized by extracellular deposition of insoluble fibrils, deriving from proteins encoded by mutated genes or normal, misfolded proteins [1,2]. Previously considered a very rare condition, amyloidosis is increasingly recognized as an important cause of cardiac disease [3]. Cardiac involvement is common in both immunoglobulin light-chain (AL) and transthyretin amyloidosis (ATTR), and is a major determinant of clinical presentation and outcome; it may manifest with left ventricular (LV) pseudohypertrophy and/or heart failure with preserved or mid-range ejection fraction (HFpEF/HFmrEF), possibly evolving towards systolic dysfunction, and sometimes accompanied by conduction disturbances or arrhythmias [1,2]. Improved management of the haematological disorder in AL amyloidosis, and new therapies targeting specific points of the pathogenic cascade of ATTR amyloidosis are expected to impact favourably on patient quality of life and outcome [4,5]. In addition to disease-modifying therapies, patients with cardiac amyloidosis (CA) require a supportive treatment for their heart disease [4,6]. Diuretics allow to reduce pulmonary and peripheral congestion, and are the most commonly used drugs. By contrast, therapies for neurohormonal antagonism, which represent the cornerstone of treatment of HF with reduced ejection fraction (HFrEF), have no established role in CA, mostly because of concerns about their safety.

The general belief is that because these patients have a stiff heart filled with amyloid deposit and severe diastolic dysfunction, conduction

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troubles and neuropathy leading to hypotension, none of the usual HFrEF drugs is safe. In particular, beta-blockers are widely perceived to be poorly tolerated or contraindicated, for example because of hypotension, conduction disturbances or impossibility of adequately increasing cardiac output (CO), especially in cases with overt restrictive pathophysiology (when CO becomes critically dependent on heart rate), and a cautious use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARBs) has been suggested, particularly in hypotensive patients [1,2]. On the other hand, these indications are based on expert opinion and no evidence from clinical trials is available.

In the present study we aimed to address this issue by searching for incidence and risk factors for adverse events or need for discontinuation of drugs for neurohormonal antagonism in a cohort of patients diagnosed with AL or ATTR amyloidotic cardiomyopathy.

2. Methods

2.1. Patient population

Data from consecutive patients diagnosed with cardiac amyloidosis (CA) at a tertiary referral centre in Italy (Fondazione Toscana Gabriele Monasterio - FTGM, Pisa, Italy) from January 2009 to January 2019 were retrieved. Only patients not enrolled in clinical trials and followed-up at the FTGM were considered.

CA was diagnosed according to validated protocols [7,10]. Patients with HF symptoms or other symptoms possibly attributed to cardiac disease (such as syncope or bradyarrhythmia) plus clinical, electrocardiographic, biohumoral or imaging (echocardiography and/or cardiac magnetic resonance - CMR) findings deemed compatible or suggestive of CA by expert readers underwent a validated diagnostic protocol including diphosphonate scintigraphy, the search for a monoclonal protein in the serum and urine, and biopsy of cardiac or extracardiac tissues when needed to confirm the diagnosis. Cardiac AL amyloidosis was diagnosed in the 2 following cases: 1) the combination of typical features on CMR and histologically proven systemic AL amyloidosis using a non-cardiac biopsy (n = 18, 55%) [8], or 2) an endomyocardial biopsy containing AL amyloid (n = 15, 45%). Cardiac ATTR amyloidosis was diagnosed with 1) grade 2 or 3 cardiac uptake on diphosphonate scintigraphy in the absence of monoclonal gammopathy (n = 37, 56%), or 2) a cardiac biopsy containing ATTR amyloid (n = 29, 44%) [7].

The study protocol conformed to the 1975 Declaration of Helsinki [11], and was approved by the Institution's human research committee. All patients provided written informed consent.

2.2. Patient management

The diagnostic workup for CA was usually performed in the inpatient setting. In the absence of any specific evidence on neurohormonal antagonists in CA, including the timing of start and up-titration, therapy with beta-blockers, followed by ACEi/ARB and MRA, was started from low doses or slowly up-titrated whenever no absolute contraindications were present (Supplemental Table 1). The type and dose of drug, and timing of up-titration were chosen based on a common protocol taking into account type of CA, symptoms, vital signs, electrocardiographic signs, echocardiographic findings, and comorbidities. Patient and caregivers were thoroughly informed about the possible adverse effects of these new therapies or dosage adjustments, and were advised to promptly report these effects, even before planned follow-up visits.

2.3. Follow-up

Patients were followed-up in a dedicated outpatient clinic on an individualized fashion, as clinically indicated. During ambulatory visits, specific attention was paid to possible adverse effects (hypotension, syncope, fatigue, symptomatic bradycardia, rhythm disorders warranting pacemaker implantation [12]) through clinical history and physical examination, home and ambulatory blood pressure measurements, electrocardiogram and biohumoral tests. The need for HF hospitalization, dose reduction or permanent drug discontinuation was decided on an individual basis.

For the present study, relevant data were retrieved from electronic health records (EHRs) in September 2019. The follow-up ended at the last visit or admission to the FTGM.

2.4. Study design and statistical analysis

The statistical analysis was performed using IBM SPSS Statistics (version 22, 2013). Normal distribution was assessed through the Kolmogorov-Smirnov test; as all variables had non-normal distribution, they were expressed as median and interquartile interval. Mean differences between groups were evaluated through the unpaired Student T test or the Mann Whitney U test, as appropriate. Uni- and multivariable logistic regression analysis was performed to search for predictors of adverse events. p values <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics at baseline

Ninety-nine patients were evaluated (72% men, median age 80 years [72,83]). All these patients were symptomatic for dyspnoea, and the majority (75%) had had previous HF hospitalizations. Thirty-three patients (33%) were diagnosed with AL amyloidosis, and 66 (67%) with ATTR amyloidosis (n = 3 with variant ATTR - v-ATTR). Median LVEF was 50%; 15 patients (15%) had HFrEF, 26 (26%) had HFmrEF, and 57 (58%) had HFpEF. Median N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP) levels were 3984 ng/L (1710-9265). Sixteen patients (16%) had a pacemaker, and 14 of them had a paced rhythm at the time of diagnosis; among the 83 non-paced patients (83%), 22 (27%) had a first-degree atrioventricular block, and 10 (12%) a left bundle branch block (Table 1).

As expected, patients with AL amyloidosis were younger, had lower arterial pressures, were more often in sinus rhythm, had a lower degree of left ventricular pseudohypertrophy, and more often a mild reduction of systolic function (left ventricular ejection fraction [LVEF] 40-49%) than those with ATTR amyloidosis (Table 1).

3.2. Therapies at study entry

At the time of diagnosis of CA, 60 patients (61%) were on beta-blockers, 63 (64%) on ACEi/ARB, and 37 (37%) on MRA. When considering median equivalent doses (Supplemental Table 2), median bisoprolol, ramipril, valsartan, and spironolactone daily doses were 2.5 mg, 5 mg, 80 mg, and 25 mg, respectively.

Therapies for neurohormonal antagonism had been prescribed as a treatment of arterial hypertension (reported by 61 patients, 62%) and/or HF, with either reduced or preserved ejection fraction; under this respect, 54 patients (54%) displayed prominent dyspnoea (New York Heart Association class III or IV), 41 (42%) had systolic dysfunction (LVEF $<50\%$), and 69 (69%) had an E/e' ratio >14.

Patients on beta blockers at baseline had higher NT-proBNP levels, and were less often on sinus rhythm than those not on beta-blockers; only minor differences reached statistical significance when comparing patients on ACEi/ARB or MRA at baseline vs. those without (Supplemental Table 3).

Table 1
Patient characteristics.

	All patientsn = 99	AL amyloidosisn = 33 (33%)	ATTR amyloidosisn = 66 (67%)	P
Men, n (%)	71 (72)	20 (61)	51 (77)	0.083
Age (years)	80 (72-83)	69 (65-76)	81 (76-82)	<0.001
BMI (kg/m^2)	25.8 (24.2-28.6)	24.6 (21.3-26.8)	25.2 (23.2-28.2)	0.369
SAP (mmHg)	120 (110-140)	110 (110-120)	128 (105-140)	0.015
DAP (mmHg)	70 (60-80)	70 (60-70)	78 (60-81)	0.036
eGFR (mL/min/1.73 m^2)	49 (39-70)	48 (36-67)	65 (37-81)	0.477
NYHA class I,II,III,IV,n(%)	18,27,37,17(18,27,37,17)	7,6,14,6(21,18,42,18)	11,21,23,11(17,32,35,17)	0.548
History of hypertension, n (%)	61 (62)	16 (49)	45 (68)	0.057
Diabetes, n (%)	12 (12)	1 (3)	11 (17)	0.050
NT-proBNP (ng/L)	3984 (1710-9265)	9483 (3833-13059)	2845 (1703-7218)	0.274
hs-TnT (ng/L)	62 (45-113)	102 (43-196)	61 (44-95)	0.072
Pacemaker, n (%)	17 (17)	3 (9)	14 (21)	0.124
ECG				
Sinus rhythm, n (%)	57 (58)	28 (85)	29 (44)	<0.001
AF/atrial flutter, n (%)	36 (36)	4 (12)	32 (49)	<0.001
Paced rhythm, n (%)	14 (14)	1 (3)	13 (20)	0.023
Heart rate (b.p.m.)	63 (59-77)	76 (60-86)	62 (58-70)	0.027
PR duration* (ms)	180 (158-205)	180 (154-196)	199 (163-214)	0.100
1st degree AV block*,n (%)	22 (22)	7 (21)	15 (23)	0.036
QRS duration* (ms)	122 (102-145)	136 (106-166)	120 (100-140)	0.170
LBBB*, n (%)	10 (10)	3 (9)	7 (11)	0.608
LAH*, n (%)	17 (17)	5 (15)	12 (18)	0.448
RBBB*, n (%)	15 (15)	4 (12)	11 (17)	0.345
2D echo				
IVS (mm)	17 (15-20)	15 (14-19)	18 (15-20)	0.005
PW (mm)	15 (13-17)	13 (12-15)	15 (14-17)	0.002
RWT	0.62 (0.52-0.84)	0.58 (0.44-0.91)	0.67 (0.54-0.84)	0.247
LVEDVi (mL/m^2)	56 (44-66)	56 (43-66)	58 (43-66)	0.047
LVESVi (mL/m^2)	23 (18-30)	24 (17-36)	24 (20-36)	0.079
LVMI (g/m^2)	170 (127-202)	157 (147-202)	183 (168-201)	<0.001
LVEF (%)	50 (42-58)	49 (45-61)	54 (49-61)	0.991
LVEF <40%, 40-49%, ≥50%, n (%)	15, 26, 57(15, 26, 58)	2, 14, 17(6, 42, 52)	13, 12, 40(20, 18, 61)	0.019
SV (mL)	52 (38-64)	49 838-62)	58 (36-74)	0.484
E/e' ratio	17 (14-21)	23 (14-29)	18 (13-20)	0.789
TAPSE (mm)	16 (13-20)	14 (13-20)	18 (15-24)	0.727

Estimated glomerular filtration rate (eGFR) was calculated through the Chronic Kidney Disease Epidemiology Collaboration equation. AF, atrial fibrillation; AL, amyloid light-chain; ATTR, amyloid transthyretin; AV, atrio-ventricular; BMI, body mass index; hs-TnT, high-sensitivity troponin T; DAP, diastolic arterial pressure; ECG, electrocardiogram; IVS, interventricular septum; LAH, left anterior hemiblock; LBBB, left bundle branch block; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMI, left ventricular mass index; NT-proBNP, N-terminal fragment of proB-type natriuretic peptide; NYHA, New York Heart Association; PM; pacemaker; PW, posterior wall; RBBB, right bundle branch block; RWT, relative wall thickness; SAP, systolic arterial pressure; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion. * patients with no paced rhythm.

3.3. Therapy after the diagnosis of cardiac amyloidosis

Immediately after the diagnosis of CA, 86 patients (87%) were on beta-blockers, 74 (75%) on ACEi/ARB, and 62 (63%) on MRA (Supplemental Table 4 and Fig. 1). Some of these patients started the therapy after the diagnosis of CA: in detail, 29 patients (29%) started a beta-blocker, 11 (11%) an ACEi/ARB, and 26 (26%) an MRA. A larger number of patients had their therapies either started or up-titrated: beta-blocker, n = 55 (56%); ACEi/ARB, n = 25 (25%); MRA, n = 39 (39%). Median daily doses of bisoprolol, ramipril, valsartan, and spironolactone after diagnosis of CA were 2.5, 5, 80, and 25 mg, respectively.

3.4. Follow-up: assessment of drug safety and tolerability

3.4.1. Whole population

Over a 16-month follow-up (7-29), patients were re-evaluated a median of 3 times (2-6), either in the outpatient or inpatient setting. Eight patients (8%) experienced hypotension, and 6 (6%) had syncope; 30 (30%) complained of fatigue, and 6 (6%) of symptomatic bradycardia; 52 (53%) underwent at least 1 HF hospitalization. Pacemaker implantation was needed in 9 patients (9%): among these cases, 4 (44%) were due to severe bradycardia (with either sinus rhythm or atrial fibrillation), and 2 (22%) to conduction disturbances or pauses lasting ≥3 seconds. Beta-blockers had to be permanently discontinued in 7 patients (7%) after a median follow-up period of 7.8 months (2.2-19.8), and 15 (15%) required dose reduction. No cases of serious hyperkalaemia (serum potassium ≥6 mEq/L) were recorded, and no patient required dose reduction or permanent discontinuation of ACEi/ARB or MRA.

3.4.2. Patients with a beta-blocker started or up-titrated after diagnosis of CA

Fifty-five patients (56%) underwent starting or up-titration of a beta-blocker. These patients did not display significant differences from the other patients, except for a higher heart rate at baseline (Supplemental Table 5). These patients did not show a higher frequency of hypotension, fatigue, syncope, symptomatic bradycardia, need for pacemaker implantation, or HF hospitalization than the other patients (Fig. 2), despite an almost significantly longer follow-up duration (19 months [9,33] vs. 13 [5-27]; p = 0.054). Three patients (6%) had to stop the drug over 8 months (6-13), and 12 patients (22%) required dose reduction.

3.4.3. Patients with a beta-blocker started after diagnosis of CA

Twenty-nine patients (29%) started a beta-blocker. Compared to the other patients, they were more often in sinus rhythm, and less often on ACEi/ARB (Supplemental Table 6). These patients did not show a higher frequency of hypotension, fatigue, syncope, symptomatic bradycardia, need for pacemaker implantation, or HF hospitalization than the other patients (Fig. 2), over a similar follow-up duration (19 months [7,39] vs. 16 [7,28]; p = 0.428). Two patients (7%) had to stop the drug

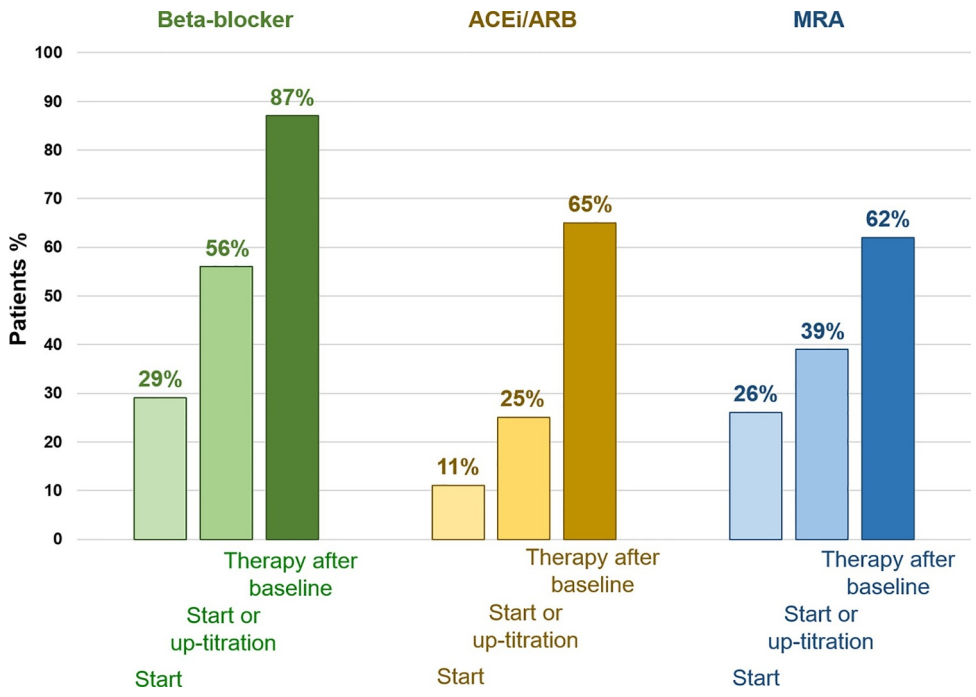

Fig. 1. Percentages of patients starting a therapy for neurohormonal antagonism or either starting or up-titrating this therapy. ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists.

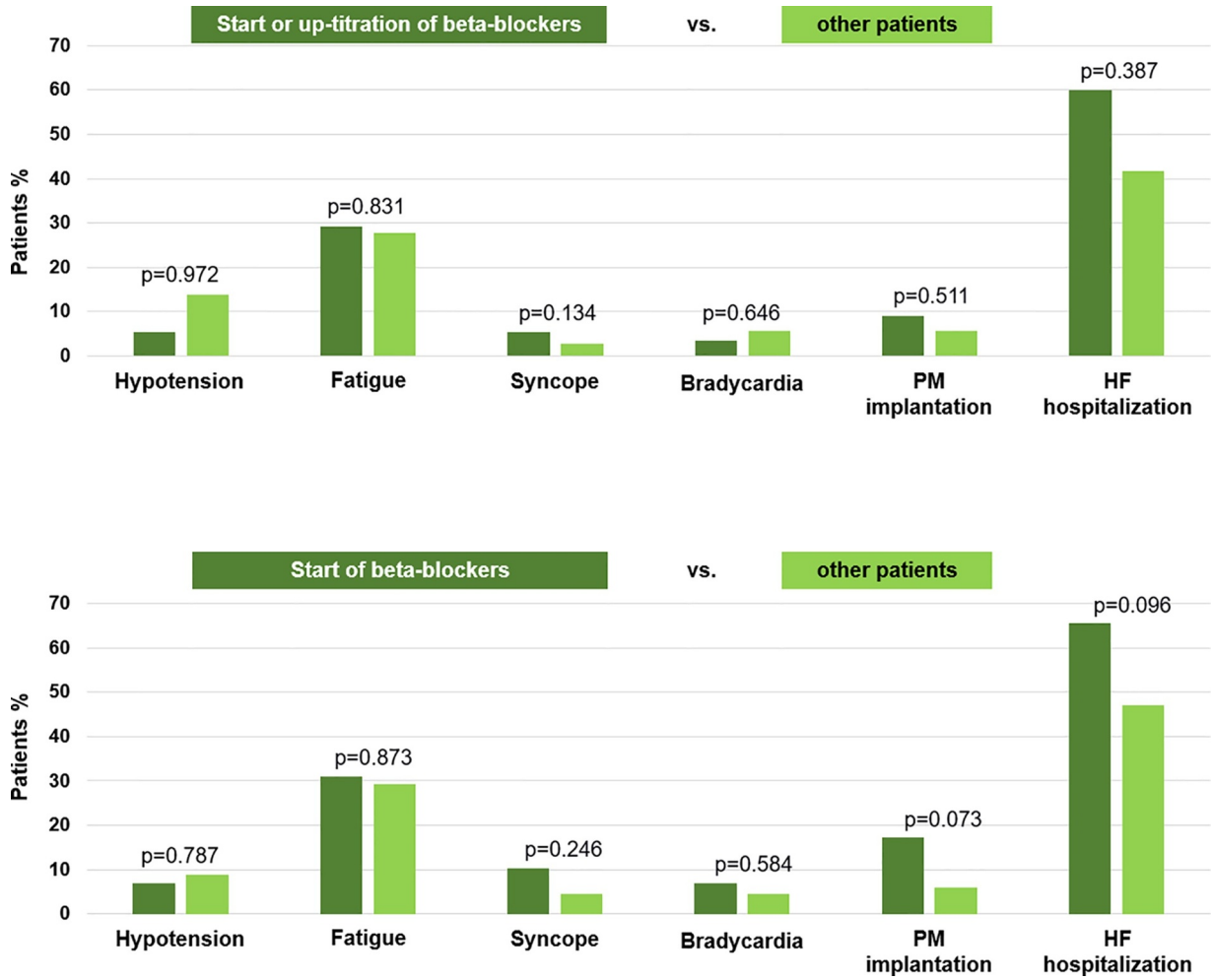

Fig. 2. Adverse events among patients starting or up-titrating a beta-blocker versus the other patients. HF, heart failure; PM, pacemaker.

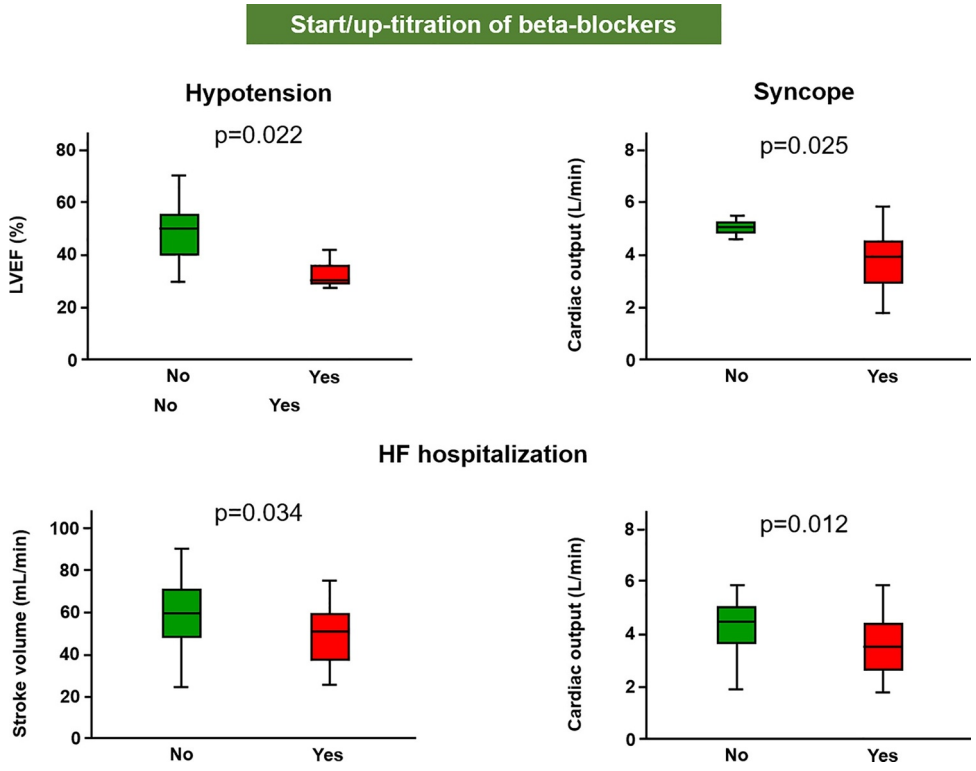

Fig. 3. Haemodynamic function and adverse events from beta-blocker therapy. HF, heart failure.

over 8 months (6-9); 6 patients (21%) required dose reduction.

3.4.4. Predictors of problems with beta-blocker therapy

In the whole population, among all baseline patient characteristics listed in Table 1, AL amyloidosis, reduced function of the left heart (demonstrated by lower stroke volume - SV - and LVEF values) and right heart (demonstrated by lower tricuspid annular plane systolic excursion) were associated with HF hospitalization, and lower systolic blood pressure (SBP) predicted the need for dose reduction. AL amyloidosis emerged also as a univariate predictor of HF hospitalization (Supplemental Table 7).

When considering patients having a beta-blocker started or up-titrated, several indices related to haemodynamic function were associated with worse tolerance to beta-blocker therapy. In detail, lower LVEF was associated with hypotension during follow-up, lower CO and diastolic arterial blood pressure with syncope, AL amyloidosis, lower SV and CO with HF hospitalization, and lower SBP with need for dose reduction (Fig. 3 and Table 4). Notably, lower SV and CO both predicted HF hospitalization independent from the type of amyloidosis (AL or ATTR; Table 4).

Due to the limited number of patients starting a beta-blocker therapy, predictors of problems with this therapy were not searched in this patient subset.

3.4.5. Patients with an ACEi/ARB or MRA started or up-titrated

Limited differences emerged when stratifying patients according to the start or up-titration of ACEi/ARB or MRA therapy (Table 3). Patients who had an ACEi/ARB or MRA being started or up-titrated did not experience more adverse events potentially related to these therapies (hypotension: $p = 0.151$ for ACEi/ARB, $p = 0.107$ for MRA; need for HF hospitalization. $p = 0.387$ for ACEi/ARB, $p = 0.126$ for MRA) than the other patients.

4. Discussion

This is the first study systematically assessing the safety and tolerability of drugs for neurohormonal antagonism in a contemporary cohort of patients with CA. Among 99 consecutive patients receiving a diagnosis of CA, as many as 87% of them were discharged on a beta-blocker, 75% on an ACEi/ARB, and 63% on an MRA. Specifically, 61% of patients were already on a beta-blocker, and 56% started on up-titrated a beta-blocker. The same percentages were 64% and 25% for ACEi/ARB, and 37% and 39% for MRA. Nonetheless, median drug doses remained equal and low (equivalent daily doses of bisoprolol, ramipril, valsartan, and spironolactone: 2.5, 5, 80, and 25 mg, respectively, before the diagnosis of CA; 2.5, 5, 80, and 25 mg, respectively, after the diagnosis of CA). Over a median 16-month follow-up, with a median of 3 re-evaluations, 53% of patients underwent at least one hospital admission because of HF. A limited percentage of patients (9%) required pacemaker implantation, and the most frequent complaint was fatigue (30% of patients). Patients starting or up-titrating a beta-blocker were not more likely to experience hypotension, fatigue, syncope, symptomatic bradycardia, neither to require pacemaker implantation or hospitalization because of HF. Among patients starting or up-titrating a beta-blocker, 21% required dose reduction, 5% stopped the drug, and 26% required dose reduction and/or discontinuation. ACEi/ARB and MRA proved better tolerated, with no cases of serious hyperkalaemia, need for permanent dose reduction or discontinuation.

Back to the ‘80s, systolic HF was considered an absolute contraindication to therapy with beta-blockers, and treatment of this condition relied on diuretics and digoxin. Following the demonstration that norepinephrine and plasma renin activity are increased in patients with HF, with higher levels predicting a worse prognosis [13], pharmacological inhibition of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) became the cornerstone of treatment of systolic HF, greatly improving the natural history of this condition [14,15]. By contrast, no trial on neurohormonal antagonism in HF with preserved ejection fraction (HFpEF) has ever yielded

positive results on hard or surrogate endpoints, for a number of reasons possibly including a less relevant role of SNS and RAAS activation [16]. On the other hand, some evidence of enhanced sympathetic nerve activity in HFpEF has emerged [17,19]. chronic activation of the SNS is known to have beneficial effects, for example promoting cardiac hypertrophy and fibrosis, as well as reducing the duration of diastole, and then the time available for ventricular filling and myocardial perfusion [20]. This conceptual framework may justify beta-blockade in HFpEF in the absence of contraindications. Similarly, angiotensin-II and aldosterone are established determinants of myocardial hypertrophy and fibrosis, and could then contribute to the progression of HFpEF [21,23]. Both ACEi/ARB and MRA may be considered on the light of these pathophysiological considerations, when patients have no hypotension or hyperkalaemia [24].

Despite the usual presentation with a hypertrophic phenotype, CA cannot be assimilated to HFpEF for many reasons, including the accumulation of amyloid fibrils causing a “pseudohypertrophy”, and the more rapid progression to systolic dysfunction in AL amyloidosis [1]. Autonomic dysfunction is frequently encountered in v-ATTR with polyneuropathy [25], and cardiac denervation has been reported in this condition [26], but we are not aware of studies investigating SNS or RAAS function in other forms of CA. A sustained activation of these axes is a common pathogenetic mechanism in systolic HF, acting as a compensatory mechanism, and it is then likely to occur also in patients with CA and systolic dysfunction, who could then benefit from therapies for neurohormonal antagonism. Among patients with HFpEF, the rationale for beta-blocking, ACEi/ARB, and MRA therapy may reside in the cardioprotective effects of these drugs, which reduce cardiomyocyte death by necrosis and apoptosis, as well as inflammation and fibrosis. Dedicated studies should explore these effects in the setting of CA, and their impact on cardiac remodelling and natural history of the disease.

While a demonstration of efficacy of these drugs is waited, we tried to address the issue of their safety and tolerability. We report that as many as 88% of patients had no absolute contraindications to beta-blockers. The percentage of patients on beta-blockers is much higher than that reported in the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), i.e. around 30% [26], suggesting that beta-blockers are often avoided because concerns about their safety rather than objective contraindications. Except for fatigue (30% of patients), only less than 10% experienced adverse effects attributable to these drugs, namely hypotension, symptomatic bradycardia, or need for pacemaker implantation. Beta-blockers were discontinued in 14% of patients, and 29% required dose reduction and/or discontinuation, most commonly in the setting of a HF hospitalization. Similar percentages were found among patients with a beta-blocker started or up-titrated; notably, these patients had no more adverse events than the other patients, despite an almost significantly longer follow-up duration. A low percentage of patients (6%) required dose discontinuation over a median timespan of almost 8 months, although over one fourth of patients needed dose reduction or drug discontinuation. Overall, these findings suggest that beta-blockade is relatively safe and well tolerated when started at low doses and slowly up-titrated according to patient response, not necessarily aiming at the highest tolerated dose as in HFrEF.

Despite the small patient number, the search for baseline characteristics associated with worse tolerance to beta-blocker therapy revealed a quite consistent association between worse haemodynamic function and adverse effects. For example, among patients who had a beta-blocker started or up-titrated, lower CO was associated with syncopal events and need for HF hospitalization, and lower blood pressure with syncope or need for dose reduction. Both lower SV and CO emerged as predictors of deteriorating haemodynamic function requiring HF hospitalization, independent from a diagnosis of AL amyloidosis (which is notoriously associated with a more rapid disease progression than ATTR amyloidosis). Notably, among patients requiring HF hospitalization, haemodynamic function at baseline displayed only a modest impairment (for example, median CO 3.5 L/min with a reference range of 4 to 8 L/min). Overall, these findings suggest that particular care should be taken when starting or up-titrating beta-blockers to patients with even initial signs of altered haemodynamic function (as demonstrated by lower SV or CO, LVEF, or blood pressures), or with AL amyloidosis.

A number of limitations to this preliminary, hypothesis-generating study must be acknowledged. First, this study was a retrospective analysis of data from a single centre, and all decisions on drug treatment with beta-blockers, ACEi/ARB, or MRA were left to treating clinicians. Propensity score-matching was not attempted for 2 reasons: 1) this type of analysis tries to account for factors advising for or against starting of a treatment with a drug with uncertain prognostic benefit (for example, aspirin for primary cardiovascular prevention, or beta-blockers in stable coronary artery disease), while in this study the presence of clear contraindications to beta-blockers, ACEi/ARB, or MRA at the time of CA diagnosis was deemed the only reason not to start or up-titrate them, and 2) the small patient number [27,28]. Second, median follow-up duration was just 16 months, and the good tolerability of therapies for neurohormonal antagonism does not necessarily persist over a longer follow-up. Third, the limited size of this patient cohort ($n = 99$) prevented a reliable assessment of the effects of treatment in several subgroups, for example 1) patients starting a therapy with beta-blocker, ACEi/ARB, or MRA vs. those already on these medications, 2) patients with AL or ATTR (the former being possibly less tolerant to therapies for neurohormonal antagonism [1], 3) patients with a pacemaker implanted at baseline vs. those without (a subgroup analysis particularly important to assess the tolerability of beta-blocker therapy), 4) patients with LVEF $< 40\%$ (who have an indication to therapies for neurohormonal antagonism according to HF guidelines [26]) vs. those with LVEF $\geq 40\%$. Additionally, a search of thresholds for LVEF, CO, SV and SBP below which is not advised to administer beta blockers was not attempted again because of the small number of patients. Third, only a small minority of patients ($n = 3$) with v-ATTR were evaluated, but autonomic dysfunction is a prominent feature of this form of amyloidosis (see above), and a different response to beta-blockers or other therapies for neurohormonal antagonism cannot be excluded. Fourth, patients were managed by cardiologists with an expertise on CA, and were carefully followed-up; a higher frequency of adverse events from therapies for neurohormonal antagonism cannot then be excluded when patients are managed by non-expert cardiologists and/or follow-up visits are less frequent. Fifth, the follow-up protocol was tailored on the individual patient, although frequent visits with thorough clinical and biohumoral evaluation were planned in all cases, with a peculiar attention to drug safety and tolerability. Sixth, the follow-up was based exclusively on data from EHRs, to precisely evaluate changes in medical therapy over time and the reasons of any change. Furthermore, only the first HF hospitalization was considered, contrary for example to the ATTR-ACT trial [27]. Fatal endpoints were not examined because any meaningful assessment of the prognostic benefit from therapies for neurohormonal antagonism would not have been possible given the limited number of patients and the fact that the vast majority of patients were being treated. Seventh, predictors of adverse events were searched through a logistic regression analysis instead of a Cox regression analysis, thus not considering the time to event. Indeed, only the timing of drug discontinuation or dose change was retrieved, also because several patient complaints (such as fatigue or symptomatic bradycardia) were difficult to precisely locate in time. Finally, the percentages of patients on beta-blockers, ACEi/ARB, or MRA at baseline seemed quite high compared to the only reference point from the literature, namely the ATTR-ACT trial (see above). This discrepancy may be attributed, at least partially, to a greater propensity to administer drugs for neurohormonal antagonism to patients with HFmrEF or HFpEF, as per institutional policy at the FTGM. To mitigate the possible confounding effect of this factor, we assessed specifically the subgroup of patients starting or up-titrating a beta-blocker, ACEi/

ARB, or MRA versus those not starting or up-titrating them.

In conclusion, drugs for neurohormonal antagonism (particularly ACEi/ARB and MRA) can be safely used in CA, provided that no contraindications are present, treatment is started at a low dose and slowly up-titrated, and patients are monitored quite closely. Beta-blockade is less well tolerated in patients with AL amyloidosis and worse haemodynamic function. Further studies, possibly with a prospective design, are warranted to confirm and expand these findings.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.05.015.

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