ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3369–3374
Published online 14 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13411

SHORT COMMUNICATION

Current patterns of beta-blocker prescription in cardiac amyloidosis: an Italian nationwide survey

Giacomo Tini[1,2], Francesco Cappelli[3], Elena Biagini[4], Beatrice Musumeci[2], Marco Merlo[5], Lia Crotti[6], Matteo Cameli[7], Gianluca Di Bella[8], Alberto Cipriani[9], Francesca Marzo[10], Federico Guerra[11], Cinzia Forleo[12], Christian Gagliardi[4], Mattia Zampieri[3], Samuela Carigi[10], Pier Filippo Vianello[1], Giulia Elena Mandoli[7], Giuseppe Ciliberti[11], Luca Lichelli[9], Davide Mariani[6], Aldostefano Porcari[5], Domitilla Russo[2], Roberto Licordari[8], Alberto Ponziani[4], Italo Porto[1,15], Federico Perfetto[3], Camillo Autore[2], Claudio Rapezzi[13,14], Giafranco Sinagra[5] and Marco Canepa[1,15]*

[1]*Department of Internal Medicine, University of Genova, Viale Benedetto XV, 10, Genova, 16132, Italy;* [2]*Cardiology, Clinical and Molecular Medicine Department, Sapienza University of Rome, Rome, Italy;* [3]*Tuscan Regional Amyloidosis Centre, Careggi University Hospital, Florence, Italy;* [4]*Cardiology Unit, St. Orsola Hospital, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy;* [5]*Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI), University of Trieste, Trieste, Italy;* [6]*Department of Cardiovascular, Neural and Metabolic Sciences, University of Milano-Bicocca, Istituto Auxologico Italiano, IRCCS, Milan, Italy;* [7]*Department of Medical Biotechnologies, Section of Cardiology, University of Siena, Siena, Italy;* [8]*Rare Cardiac Disease Center, Cardiology Unit, University of Messina, Messina, Italy;* [9]*Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy;* [10]*Cardiology Unit, Infermi Hospital, Rimini, Italy;* [11]*Cardiology and Arrhythmology Clinic, Marche Polytechnic University, University Hospital "Ospedali Riuniti Umberto I -Lancisi - Salesi", Ancona, Italy;* [12]*Cardiology Unit, Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, University Hospital Policlinico Consorziale, Bari, Italy;* [13]*University Cardiological Center, University of Ferrara, Ferrara, Italy;* [14]*Maria Cecilia Hospital, GVM Care & Research, Ravenna, Italy; and* [15]*Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino – IRCCS Italian Cardiovascular Network, Genova, Italy*

Abstract

Aims The use of beta-blocker therapy in cardiac amyloidosis (CA) is debated. We aimed at describing patterns of beta-blocker prescription through a nationwide survey.

Methods and results From 11 referral centres, we retrospectively collected data of CA patients with a first evaluation after 2016 (n = 642). Clinical characteristics at first and last evaluation were collected, with a focus on medical therapy. For patients in whom beta-blocker therapy was started, stopped, or continued between first and last evaluation, the main reason for beta-blocker management was requested. Median age of study population was 77 years; 81% were men. Arterial hypertension was found in 58% of patients, atrial fibrillation (AF) in 57%, and coronary artery disease in 16%. Left ventricular ejection fraction was preserved in 62% of cases, and 74% of patients had advanced diastolic dysfunction. Out of the 250 CA patients on beta-blockers at last evaluation, 215 (33%) were already taking this therapy at first evaluation, while 35 (5%) were started it, in both cases primarily because of high-rate AF. One-hundred-nineteen patients (19%) who were on beta-blocker at first evaluation had this therapy withdrawn, mainly because of intolerance in the presence of heart failure with advanced diastolic dysfunction. The remaining 273 patients (43%) had never received beta-blocker therapy. Beta-blockers usage was similar between CA aetiologies. Patients taking vs. not taking beta-blockers differed only for a greater prevalence of arterial hypertension, coronary artery disease, AF, and non-restrictive filling pattern ($P < 0.01$ for all) in the former group.

Conclusions Beta-blockers prescription is not infrequent in CA. Such therapy may be tolerated in the presence of co-morbidities for which beta-blockers are routinely used and in the absence of advanced diastolic dysfunction.

Keywords Cardiac amyloidosis; Beta-blockers; Transthyretin; Light chains; Heart failure

Received: 7 January 2021; Revised: 11 April 2021; Accepted: 28 April 2021
**Correspondence to: Marco Canepa, Cardiovascular Unit, IRCCS Ospedale Policlinico San Martino IRCCS, Genova, Italy, and Department of Internal Medicine, University of Genova, Viale Benedetto XV, 10, 16132 Genova GE, Italy. Phone: +390105555834; Fax: +390105556318. Email: marco.canepa@unige.it*

© 2021 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Introduction

Cardiac amyloidosis (CA) is a condition increasingly recognized.[1] Progressive amyloid myocardial infiltration by light-chain (AL) or transthyretin (ATTR, either mutant, ATTRv, or wild-type, ATTRwt) proteins causes a variety of cardiac manifestations, including heart failure (HF) and arrhythmias.[2,3] Both atrial fibrillation (AF) and brady-arrhythmias are common in CA.[4–6] This is particularly true for ATTRwt patients, who may present such conditions as co-morbidities of their older age.

The use of beta-blocker therapy in CA is debated.[7,8] CA often presents a restrictive HF pathophysiology with preserved left ventricular ejection fraction (LVEF), condition in which beta-blockers lack of efficacy or may even be counterproductive.[9] Moreover, a previous study found worse outcomes in ATTRv patients taking beta-blocker and angiotensin converting enzyme-inhibitor (ACEi) therapy, and no benefit in ATTRwt.[10] Nevertheless, more recent real-world analyses have shown that beta-blockers in CA are frequently prescribed[11] and may be well-tolerated, with accurate patients' selection.[12] Finally, CA may also coexist with age-related co-morbidities in which beta-blockers are proven beneficial, in particular coronary artery disease (CAD).

The aim of this study was to investigate and describe patterns of beta-blockers prescription in a contemporary cohort of CA.

Methods

From 11 Italian amyloidosis referral centres, we retrospectively collected data of all CA patients with a first evaluation after 1 January 2016 and at least one follow-up visit, regardless of their vital status at the time of survey data collection. In the year 2016, Gillmore and colleagues[13] published an algorithm validating the use of bone scintigraphy for the non-invasive diagnosis of ATTR CA, which is still considered the reference standard. Thus, we decided to include in our analysis only CA patients diagnosed according to this algorithm, which has been adopted by all centres participating in this survey. Collection started on 8 June 2020, and database was locked on 15 September 2020. Two larger centres contributed with 317 patients (Florence, n = 178; Bologna, n = 139), whereas the remaining nine with 325 patients, for a total of 642 CA patients. Demographics, clinical, and instrumental characteristics at first and last evaluation at each centre were collected, with a detailed section dedicated to HF medical therapy, including beta-blockers, ACEi, angiotensin receptor blockers (ARB), mineral corticoid receptor antagonists (MRA), and loop diuretics. In particular, the status and dosage of beta-blocker therapy at first and last evaluation were examined; for patients in whom beta-blocker therapy was continued, started or stopped between first and last evaluation, the main reason for beta-blocker management was requested. Among the proposed options, reasons for beta-blocker therapy to be continued or started were the following: (i) high-rate AF, as average heart rate per minute $>$100; (ii) ventricular arrhythmias, as the presence of sustained and/or non-sustained ventricular tachycardia and/or frequent premature ventricular complexes at electrocardiography; (iii) left ventricular systolic dysfunction, as a LVEF $\leq$50%; (iv) arterial hypertension, defined as either antihypertensive medications use and/or systolicblood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg; (v) ischaemic heart disease, defined as a documented previous myocardial infarction and/or the existence of angiographic evidence of significant coronary stenosis. Reasons for beta-blocker therapy to be stopped were the following: (i) intolerance in the context of HF signs and symptoms, with an advanced diastolic dysfunction pathophysiology defined by the presence of a pseudonormal or restrictive transmitral flow pattern, associated with increased left ventricular filling pressures and left atrial enlargement[14]; (ii) bradycardia, defined as a heart rate below 60 b.p.m.; (iii) arterial hypotension, defined as systolic blood pressure $<$110 mmHg; (iv) atrioventricular conduction disturbances. All patients signed at each institution an informed consent for the use of their anonymized aggregated data for research purposes. Data were collected using the Research Electronic Data Capture (REDCap) data management platform. One-way ANOVA, χ^2, and Fisher's exact tests were used as appropriate for descriptive statistics.

Results

Characteristics of the 642 patients at their last evaluation are displayed in *Table 1*, overall and by type of CA. Date of the first evaluation spanned from 4 January 2016 to 7 June 2020, whereas date of last evaluation from 21 September 2016 to 14 September 2020, with a median time of follow-up of 419 days (range 28–1662). ATTRwt was the most prevalent aetiology of CA (58%), with a steady yearly increase in the number of diagnoses (*Table 1*). Median age of overall population was 77 years, and 81% were men, with an older age and a greater male predominance in the ATTRwt group. More than a half of the study population had a history of arterial hypertension and of AF, with a significantly greater prevalence in the ATTRwt group. LVEF was preserved in 62% of the study sample, but 74% of patients had advanced diastolic dysfunction, which was particularly found in ATTRwt patients (*Table 1*). Diuretic therapy was prescribed to most patients, and especially to those with ATTRwt, whereas ACEi/ARB to 44% and MRA to 40%, without marked differences between groups. Pacemaker implantation was more common in ATTRwt (17%, vs. 7% in AL and 8% in ATTRv).

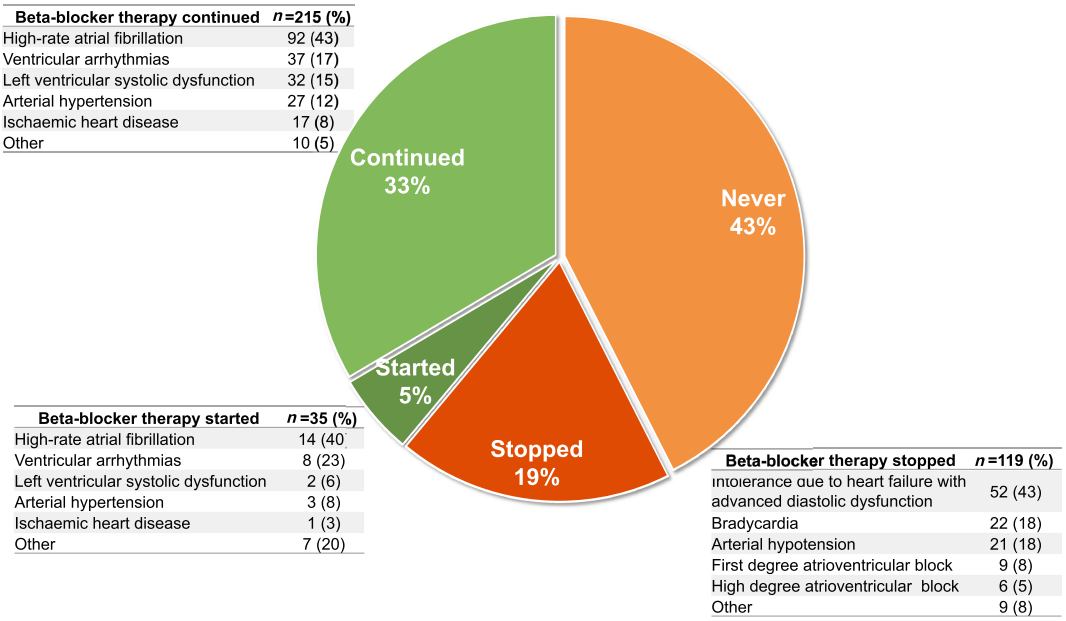
Table 1 Characteristics of study population at last evaluation

	Overall *n* = 642 (%)	AL *n* = 167 (%)	ATTRv *n* = 100 (%)	ATTRwt *n* = 375 (%)	
Age (median, range; years)	77 (34–96)	68 (44–96)	72 (34–88)	81 (54–96)	**<0.0001**
Year of first evaluation					
2016	81	23	20	38	
2017	112	34	17	61	
2018	178	44	26	108	
2019	224	55	34	135	
2020 (January–June)	47	11	3	33	
Time from first evaluation (range; days)	419 (28–1662)	382 (34–1662)	483 (113–1477)	406 (28–1638)	**0.04**
Gender					**<0.0001**
Males	519 (81)	109 (65)	71 (71)	339 (90)	
Females	123 (19)	58 (35)	29 (29)	36 (10)	
History of arterial hypertension	374 (58)	80 (48)	57 (57)	237 (63)	**0.004**
History of coronary artery disease	100 (16)	15 (9)	10 (10)	75 (20)	**0.001**
History of atrial fibrillation	364 (57)	73 (44)	38 (38)	253 (68)	**<0.0001**
Cardiac device	127 (20)	20 (12)	13 (13)	94 (25)	**0.02**
Pacemaker	*82 (13)*	*11 (7)*	*8 (8)*	*63 (17)*	
ICD	*31 (5)*	*8 (5)*	*3 (3)*	*20 (5)*	
CRT-P/D	*14 (2)*	*1 (<1)*	*2 (2)*	*11 (3)*	
Clinical status					
NYHA functional class					**0.03**
I/II	405 (63)	93 (56)	71 (71)	241 (64)	
III/IV	237 (37)	74 (44)	29 (29)	134 (36)	
Mean systolic blood pressure (mmHg, ±SD)	120 ± 18	116 ± 20	122 ± 19	121 ± 17	**0.02**
Mean heart rate (b.p.m., ±SD)	75 ± 14	76 ± 13	74 ± 12	75 ± 14	0.78
ECG and echocardiography					
Heart rhythm					**<0.0001**
Sinus rhythm	348 (54)	127 (76)	71 (71)	150 (40)	
Atrial fibrillation/flutter	245 (38)	35 (21)	22 (22)	188 (50)	
Pacemaker stimulated	49 (8)	5 (3)	7 (7)	37 (10)	
Left ventricular ejection fraction					0.76
<40%	95 (15)	24 (14)	13 (13)	58 (16)	
40–49%	147 (23)	36 (22)	20 (20)	91 (24)	
≥50%	400 (62)	107 (64)	67 (67)	226 (60)	
Diastolic function					**<0.0001**
Normal	27 (4)	10 (6)	11 (11)	6 (2)	
Abnormal relaxation	142 (22)	48 (29)	26 (26)	68 (18)	
Pseudonormal	215 (34)	44 (26)	31 (31)	140 (37)	
Restrictive	258 (40)	65 (39)	32 (32)	161 (43)	
Cardiovascular therapy					
Loop diuretics	545 (85)	136 (81)	70 (70)	339 (90)	**<0.0001**
Beta-blocker	250 (39)	62 (37)	37 (37)	151 (40)	0.72
Beta-blocker dose ≥50%	*52 (21)*	*12 (19)*	*3 (8)*	*37 (25)*	
ACEi/ARB	276 (44)	68 (41)	51 (51)	157 (42)	0.21
MRA	258 (40)	70 (41)	28 (28)	160 (43)	**0.03**
Combinations with beta-blocker					0.69
Beta-blocker only	60 (9)	19 (11)	9 (9)	32 (8)	
Beta-blocker and ACEi/ARB	75 (12)	16 (10)	15 (15)	44 (12)	
Beta-blocker and MRA	70 (11)	17 (10)	7 (7)	46 (12)	
Beta-blocker, ACEi/ARB and MRA	45 (7)	10 (6)	6 (6)	29 (8)	
Patterns of beta-blocker prescription					**<0.0001**
Never beta-blocker	273 (43)	87 (52)	50 (50)	136 (36)	
Stopped beta-blocker	119 (19)	18 (11)	13 (13)	88 (24)	
Started beta-blocker	35 (5)	14 (8)	9 (9)	12 (3)	
Continued beta-blocker	215 (33)	48 (29)	28 (28)	139 (37)	

ACEi/ARB, ACE inhibitor/angiotensin receptor blocker; CRT-P/D, cardiac resynchronization therapy without or with defibrillator; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonists; NYHA, New York heart Association.

Out of the 250 CA patients on beta-blockers at last evaluation, 215 (33% of the overall population) were already taking this therapy at first evaluation (i.e. continued beta-blocker), primarily because of high-rate AF, ventricular arrhythmias, or left ventricular systolic dysfunction (*Figure 1*). In the remaining 35 CA patients (5%), beta-blockers were started after first evaluation during follow-up (i.e. started beta-blocker), primarily because of high-rate AF or ventricular arrhythmias. Of the 392 CA patients who were not taking beta-blocker at last evaluation, 273 (43%) had never received beta-blocker therapy. On the contrary, 119 (19%) patients who were on beta-blocker at first evaluation had this therapy

Figure 1 Patterns of beta-blocker therapy prescription.



Beta-blocker therapy continued	*n* =215 (%)
High-rate atrial fibrillation	92 (43)
Ventricular arrhythmias	37 (17)
Left ventricular systolic dysfunction	32 (15)
Arterial hypertension	27 (12)
Ischaemic heart disease	17 (8)
Other	10 (5)

Beta-blocker therapy started	*n* =35 (%)
High-rate atrial fibrillation	14 (40
Ventricular arrhythmias	8 (23)
Left ventricular systolic dysfunction	2 (6)
Arterial hypertension	3 (8)
Ischaemic heart disease	1 (3)
Other	7 (20)

Beta-blocker therapy stopped	*n* =119 (%)
Intolerance due to heart failure with advanced diastolic dysfunction	52 (43)
Bradycardia	22 (18)
Arterial hypotension	21 (18)
First degree atrioventricular block	9 (8)
High degree atrioventricular block	6 (5)
Other	9 (8)

withdrawn at follow-up (i.e. stopped beta-blocker), mainly because of intolerance in the presence of HF with advanced diastolic dysfunction pathophysiology. Distribution of reasons for which beta-blocker therapy was continued, started, or stopped are further detailed in *Figure 1*. Other less frequent reasons for beta-blocker interruption included asthenia (n = 3), initiation of therapy with digoxin (n = 1), and restoration of sinus rhythm after AF (n = 1), whereas for initiation or continuation were other supraventricular arrhythmias (n = 5), outflow tract obstruction (n = 1), and angina (n = 1).

Beta-blockers usage was similar between CA aetiologies at last evaluation. However, patterns of prescription varied by type of CA (*Table 1*). Specifically, half of patients in the AL and ATTRv groups never received beta-blockers (vs. 36% in the ATTRwt), but beta-blockers were more frequently stopped in the ATTRwt group (24%, vs. 11% in AL and 13% in ATTRv).

The distribution of cardiac amyloidosis aetiologies was similar in the two larger cohorts of Bologna and Firenze (in Bologna: 13% AL, 10% ATTRv, 77% ATTRwt; in Firenze: 16% AL, 14% ATTRv, 70% ATTRwt, P = 0.45), whereas a greater prevalence of AL was found in the cohort from other remaining centres (36% AL, 20% ATTRv, 44% ATTRwt, P = 0.001 as compared with Bologna and Firenze). These three cohorts were similar in terms of prevalence of atrial fibrillation (55% vs. 57% vs. 55%) and coronary artery disease (15% vs. 20% vs. 14%, $P > 0.05$ for all), with only a lower prevalence of arterial hypertension in Firenze (68% vs. 48% vs. 60%, P = 0.03). Nonetheless, rates of beta-blockers prescription were similar across the three cohorts at last evaluation (45% vs. 33% vs. 40%, P = 0.25).

Patients taking vs. not taking beta-blocker therapy at last evaluation differed only for a greater prevalence of arterial hypertension (67% vs. 53%), coronary artery disease (20% vs. 13%), AF (66% vs. 51%), and non-restrictive filling pattern (64% vs. 57%, $P < 0.01$ for all) in the former group.

Discussion

In this sizable nationwide cohort, we found that prescription of beta-blockers was not infrequent across all CA aetiologies. About 40% of patients were on beta-blocker therapy at last evaluation, which is consistent with previous real-world[11] and trial analyses.[15] It appears that prescription of beta-blockers in CA is mainly driven by co-morbidities and AF, and not by the amyloidotic cardiomyopathy *per se*.

Both AF and brady-arrhythmias have been reported to be highly prevalent in CA, especially in ATTRwt patients.[4,6,16] High-rate AF was the most common reason for beta-blockers prescription in our study, followed by ventricular arrhythmias. On the contrary, the impact of brady-arrhythmias on beta-blocker therapy interruption was relatively limited. This finding highlights the importance of a better understanding of the CA arrhythmic profile.

Up to 60% of CA patients never used (mostly AL and ATTRv) or stopped beta-blockers (most commonly ATTRwt). This happened primary due to intolerance in the presence of HF with advanced diastolic dysfunction pathophysiology. It is in fact well acknowledged that in the context of a fixed stroke volume due to restrictive left ventricular physiology,

higher heart rate is required to maintain cardiac output.[8,9] Clearly, other mechanisms are also likely to play a role in the intolerance to beta-blockers, because advanced diastolic dysfunction was present in 74% of our sample, and in some of these CA patients, beta-blockers therapy was safely delivered. It is however worth of note that, when prescribed, beta-blockers were effectively up-titrated in only 21% of cases (*Table 1*). More in general, despite also ACEi/ARBs and MRA were prescribed similarly to beta-blockers in about 40% of CA patients, the diverse combinations of these therapies were found in 6–15% of cases. Thus, overall, the tolerability of HF directed therapies in CA may be limited, and clearly, patients' selection and accurate dosage optimization are fundamental.[10,12] In the context of AL and ATTRv, autonomic dysfunction may also play a role.[2,3]

Finally, using a contemporary cohort of CA, we describe for the first time how ATTRwt is becoming the most common CA aetiology in Italy, with a steadily yearly increase in the number of diagnoses. Despite this possibility had previously been hypothesized, data in this regard are lacking.[17] Our results, informative of HF medications patterns of use in CA, are even more important in consideration of this growing CA population.

Some shortcomings of our work should be acknowledged. This was a survey focused on assessing and comparing prescription of beta-blockers at first vs. last evaluations, and as such, information regarding longitudinal modifications of that therapy (i.e., up-titration or down-titration over clinical course) were not retrieved. Dosage of drugs was reviewed only for beta-blockers and not for other HF drugs. Due to the nature of data collection, we cannot exclude that unselected or undifferentiated variables influenced our results (i.e. AL patients' status and chemotherapy regimens; electrocardiographic parameters such as differentiation of premature ventricular complexes from non-sustained or sustained ventricular tachycardia; echocardiographic indexes such as those of right ventricle function). Taking into considerations these aspects, the impact of beta-blocker therapy on outcomes could not be appropriately judged and was therefore not investigated in the present survey.

Conclusions

Beta-blockers prescription is not infrequent in CA. Such therapy may be tolerated particularly in the presence of co-morbidities for which beta-blockers are routinely used and in the absence of restrictive diastolic dysfunction. High-rate AF and ventricular arrhythmias were the two main reason for beta-blockers usage, while bradycardia or atrio-ventricular blocks accounted for less than one third of beta-blocker therapy interruption.

Conflict of interest

All authors declare they have no conflict of interest in relation to this study.

References

1. Gilstrap LG, Dominici F, Wang Y, El-Sady MS, Singh A, Di Carli MF, Falk RH, Dorbala S. Epidemiology of cardiac amyloidosis-associated heart failure hospitalizations among fee-for-service medicare beneficiaries in the United States. *Circ Heart Fail* 2019; **12**: e005407.
2. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. *J Am Coll Cardiol* 2016; **68**: 1323–1341.
3. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, Berk JL, Plante-Bordeneuve V, Schmidt HHJ, Merlini G. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol* 2015; **66**: 2451–2466.
4. Cappelli F, Vignini E, Martone R, Perlini S, Mussinelli R, Sabena A, Morini S, Gabriele M, Taborchi G, Bartolini S, Lossi A, Nardi G, Marchionni N, Di Mario C, Olivotto I, Perfetto F. Baseline ECG features and arrhythmic profile in transthyretin versus light chain cardiac amyloidosis. *Circ Heart Fail* 2020; **13**: e006619.
5. Cappelli F, Tini G, Russo D, Emdin M, Del Franco A, Vergaro G, Di Bella G, Mazzeo A, Canepa M, Volpe M, Perfetto F, Autore C, Di Mario C, Rapezzi C, Musumeci MB. Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation. *Amyloid* 2021; **28**: 12–18.
6. Donnellan E, Wazni OM, Saliba WI, Hanna M, Kanj M, Patel DR, Wilner B, Kochar A, Jaber WA. Prevalence, incidence, and impact on mortality of conduction system disease in transthyretin cardiac amyloidosis. *Am J Cardiol* 2020; **128**: 140–146.
7. Emdin M, Aimo A, Rapezzi C, Fontana M, Perfetto F, Seferović PM, Barison A, Castiglione V, Vergaro G, Giannoni A, Passino C, Merlini G. Treatment of cardiac transthyretin amyloidosis: an update. *Eur Heart J* 2019; **40**: 3699–3706.
8. Giancaterino S, Urey MA, Darden D, Hsu JC. Management of arrhythmias in cardiac amyloidosis. *JACC Clin Electrophysiol* 2020; **6**: 351–361.
9. Seferović PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, Felix SB, Arbustini E, Caforio ALP, Farmakis D, Filippatos GS, Gialafos E, Kanjuh V, Krljanac G, Limongelli G, Linhart A, Lyon AR, Maksimović R, Miličić D, Milinković I, Noutsias M, Oto A, Oto Ö, Pavlović SU, Piepoli MF, Ristić AD, Rosano GMC, Seggewiss H, Ašanin M, Seferović JP, Ruschitzka F, Čelutkiene J, Jaarsma T, Mueller C, Moura B, Hill L, Volterrani M, Lopatin Y, Metra M, Backs J, Mullens W, Chioncel O, Boer RA, Anker S, Rapezzi C, Coats AJS, Tschöpe C. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; **21**: 553–576.
10. aus dem Siepen F, Hein S, Bauer R, Katus HA, Kristen AV. Standard heart failure medication in cardiac transthyretin amyloidosis: useful or harmful? *Amyloid* 2017; **24**: 132–133.

11. Canepa M, Tini G, Musumeci B, Cappelli F, Milandri A, Mussinelli R, Autore C, Perfetto F, Rapezzi C, Perlini S. Real-world versus trial patients with transthyretin amyloid cardiomyopathy. *Eur J Heart Fail* 2019; **21**: 1479–1481.
12. Aimo A, Vergaro G, Castiglione V, Rapezzi C, Emdin M. Safety and tolerability of neurohormonal antagonism in cardiac amyloidosis. *Eur J Intern Med* 2020; **80**: 66–72.
13. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016; **133**: 2404–2412.
14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1321–1360.
15. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018; **379**: 1007–1016.
16. Longhi S, Quarta CC, Milandri A, Lorenzini M, Gagliardi C, Manuzzi L, Bacchi-Reggiani ML, Leone O, Ferlini A, Russo A, Gallelli I, Rapezzi C. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence, incidence, risk factors and prognostic role. *Amyloid* 2015; **22**: 147–155.
17. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, Salvi F, Maurer MS. Cardiac amyloidosis: the great pretender. *Heart Fail Rev* 2015; **20**: 117–124.