Editorial for the article: Hospitalization-based epidemiology of systemic and cardiac amyloidosis in the Veneto Region, Italy

1. Introduction

Cardiac amyloidosis (CA) is a progressive infiltrative disease caused most commonly by the deposition of misfolded, cleaved and aggregated monoclonal immunoglobulin free light chain (AL) or transthyretin (ATTR) proteins in the myocardial extracellular space [1]. Recent advances in imaging techniques and the development of an algorithm for non-invasive confirmation of ATTR-CA [2] have transformed the diagnosis of this condition. Although it has been traditionally considered a rare and inexorably fatal condition, CA now is an increasingly recognized cause of heart failure (HF) and mortality worldwide [3]. CA has been identified among a) 13% of patients over the age of 60 years with evidence of thick left ventricle ($\geq$ 12 mm) admitted to the hospital due to worsening HF; b) 14% of patients with HF with preserved ejection fraction (HFpEF) of unclear aetiology undergoing endomyocardial biopsy; and 15% of patients with HFpEF and a left ventricular wall thickness above 14 mm [3] (Table 1). Although major steps have been taken towards better definition of CA prevalence, the epidemiological figure of this condition is still far from being elucidated beyond regional registries [4,5] and it clearly represents a contemporary challenge.

In the last issue of the International Journal of Cardiology, De Michieli et al. [6] provide novel data on the epidemiology of systemic amyloidosis and CA in the Veneto region of Italy from 2010 to 2020, with particular emphasis on the impact of this condition on hospitalization for decompensated HF. This retrospective observational study used International Classification of Diseases (ICD-9) codes available in hospital discharge summaries to identify amyloidosis-related hospitalizations (AH), defined as any hospitalization reporting ICD-9 code for amyloidosis as a primary or secondary diagnosis. The Authors identified discharge summaries with principal or secondary ICD-9 codes for HF, cardiomyopathy or arrhythmia, and classified them as CA-related hospitalizations [6]. Despite several methodological limitations, fairly addressed by the Authors, the study provides some interesting insights on the real-word impact of systemic amyloidosis and CA on the health care system.

2. Amyloidosis-related hospitalizations

The number of AH steadily increased over time, especially among men above 65 years of age along with that of discharge records with an ICD-9 code for amyloidosis. There was a 17% annual increase in AH from 2015 to 2020, which corresponded to an AH incidence of 23.5 per million inhabitants in the region. These findings are in line with national [5] and international [7] studies reporting a progressive increase in the number of patients with AL and ATTR amyloidosis, mainly driven by greater disease awareness and broader access to diagnostic tools [1].

The use of general ICD-9 codes for amyloidosis did not allow to accurately discriminate between ATTR and AL amyloidosis and the Authors could only report on the global burden of systemic amyloidosis. To partly overcome this limitation, a sub-analysis in the group of patients with an age below and over 65 years was carried out, assuming that AL amyloidosis would be more common among patients younger that 65 years and ATTR amyloidosis among those older than 65 years [6]. Notably, the rates of AH remained stable for patients below 65 years of age while greater AH rates were observed for subjects older that 65 years. These findings are in line with recent epidemiological data from Zampieri et al. [5] in the Tuscany region in Italy where the incidence of patients diagnosed with AL amyloidosis has remained stable over time.

3. CA-related hospitalization

Data on CA-related hospitalization was only available for 2020 and for the overall study period, but not for each year, thus limiting the possibility to provide information on incidence rates of CA-related hospitalizations. From 2010 to 2020, there were 556 cases of CA-related hospitalizations in the Veneto region. In 2020, annual hospitalized prevalent cases of CA-related hospitalizations accounted for 159 cases of the 228 cases observed between 2010 and 2020, which corresponded to a proportion of 70% of cases. These patients were mostly men and older than 65 years, in keeping with the clinical phenotype of ATTR amyloidosis [8]. These findings demonstrate that enhanced awareness of disease, recognition of clinical and instrumental red flags coupled with advances in non-invasive cardiac imaging have exponentially increased the number of patients diagnosed with CA, especially over the last 3 to 5 years [9,10].

4. CA and carpal tunnel syndrome

The association between CA, mostly ATTR, and carpal tunnel syndrome (CTS) is well established [3]. For this reason, De Michieli et al. [6] pushed their epidemiological investigation beyond by identifying a population of patients with possible CA-related hospitalizations based on the presence of an ICD-9 code for 1) carpal tunnel release surgery, and 2) a subsequent code for cardiomyopathy and/or HF. Patients with multiple CTS release surgeries and an ICD-9 code for cardiomyopathy and/or HF during follow up had a substantially higher risk of underlying CA and were more frequently men than women (7.1% vs 3.9%, respectively). Again, that would be more in keeping with ATTR

Table 1
ATTR-CA, Transthyretin Cardiac Amyloidosis; CA, Cardiac Amyloidosis; HF, Heart Failure; HFmrEF, Heart Failure with mid range Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; LVH, Left Ventricular Hypertrophy; LVWT, Left Ventricular Wall Thickness.

Authors	Type of study	Clinical setting	N. of patients/ hospitalization	Prevalence of CA
Göbel et al. [11]	Retrospective, observational, multicenter	HF hospitalizations	5,478,835 hospitalizations	1.87 hospitalizations per 100,000 German population
Su Yun See et al. [12]	Meta-analysis	General HF	3303 patients across 11 studies	13.7% in overall HF 15.1% in HFpEF 11.3% in HFrEF
AbouEzzeddine et al. [13]	Prospective observational, monocenter	HFpEF, LVWT ≥12 mm, ≥60 years	268 patients screened for CA	6.3% (ATTR-CA)
Devesa et al. [14]	Prospective, observational, monocenter	HFpEF without LVH	58 patients screened for CA	5.2%
Ruiz-Hueso et al. [15]	Prospective, observational, multicenter	HF patients, LVWT>12 mm, ≥ 65 years	453 patients	20.1%
González-López et al. [16]	Prospective, observational monocenter	HFpEF, LVWT ≥12 mm, ≥60 years	120 patients	13.3%
Hahn et al. [17]	Prospective, observational monocenter	HFpEF	108 patients	14.0%
Goland et al. [18]	Prospective, observational monocenter	HFrEF/HFmrEF	76 patients	9.3%

amyloidosis as predominant form of amyloidosis [8].

5. Future directions

Hospitalization for decompensated HF represents an important outcome measure on health systems. Most studies assessing the effect of a specific treatment, either a drug or an electrical therapy, on HF hospitalization used time to first event analyses, thus focusing only on the first hospital admission for decompensated HF. However, the burden of repeated HF hospitalization might be substantially high among patients with particular cardiac diseases such as CA. *De Michieli* et al has to be commended on the statistical design of the study as only a minority of researchers attempt to incorporate recurrent HF hospitalizations in the statistical analyses of their data. This study paves the way for a greater understanding of the effect of HF hospitalization for patients with CA and health services.

In conclusion, the study by *De Michieli* et al. increases the current knowledge on the epidemiology of amyloidosis in Northeastern Italy, providing novel evidence on the impact of amyloidosis and CA on health care system. Further studies based on disease-specific registries on regional and national levels are needed to better define the prevalence and incidence of CA-related hospitalizations and to differentiate epidemiological trends for ATTR-CA and AL-CA in Italy.

Disclosure statement

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

CRediT authorship contribution statement

Aldostefano Porcari: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. **Marco Pozzan:** Writing – original draft, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131862.

References

[1] A. Porcari, M. Fontana, J.D. Gillmore, Transthyretin cardiac amyloidosis, Cardiovasc. Res. 118 (18) (2023) 3517–3535.
[2] J.D. Gillmore, M.S. Maurer, R.H. Falk, et al., Nonbiopsy diagnosis of cardiac transthyretin amyloidosis, Circulation. 133 (24) (2016) 2404–2412.
[3] A. Aimo, M. Merlo, A. Porcari, et al., Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies, Eur. J. Heart Fail. 24 (12) (2022) 2342–2351.
[4] M. Russo, L. Obici, I. Bartolomei, et al., ATTRv amyloidosis Italian registry: clinical and epidemiological data, Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis. 27 (4) (2020) 259–265.
[5] M. Zampieri, G. Nardi, G. Del Monaco, et al., Changes in the perceived epidemiology of amyloidosis: 20 year-experience from a tertiary referral Centre in Tuscany, Int. J. Cardiol. 335 (2021) 123–127.
[6] L. De Michieli, G. Stoppa, G. Sinigiani, et al., Hospitalization-based epidemiology of systemic and cardiac amyloidosis in the Veneto region, Italy, Int. J. Cardiol. (2024) 131804, https://doi.org/10.1016/j.ijcard.2024.131804.
[7] S. Ravichandran, H.J. Lachmann, A.D. Wechalekar, Epidemiologic and survival trends in amyloidosis, 1987–2019, N. Engl. J. Med. 382 (16) (2020) 1567–1568.
[8] A. Porcari, Y. Razvi, A. Masi, R. Patel, A. Ioannou, M.U. Rauf, et al., Prevalence, characteristics and outcomes of older patients with hereditary versus wild-type transthyretin amyloid cardiomyopathy, Eur. J. Heart Fail. 25 (4) (2023) 515–524.
[9] A. Porcari, G. Sinagra, J.D. Gillmore, M. Fontana, P.N. Hawkins, Breakthrough advances enhancing care in ATTR amyloid cardiomyopathy, Eur. J. Intern. Med. (2024), https://doi.org/10.1016/j.ejim.2024.01.001.
[10] A. Porcari, M. Fontana, M. Canepa, et al., Clinical and prognostic implications of right ventricular uptake on bone scintigraphy in transthyretin amyloid cardiomyopathy, Circulation (2024), https://doi.org/10.1161/CIRCULATIONAHA.123.066524.

Aldostefano Porcari[a,b,c,*], Marco Pozzan[b,c]
[a] *National Amyloidosis Centre, Division of Medicine, University College London, London, United Kingdom*
[b] *Centre for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy*
[c] *European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart, Italy*

[*] Corresponding author at: National Amyloidosis Centre, Division of Medicine, University College London, Royal Free Campus, Rowland Hill St, London NW1 2PF, United Kingdom.
E-mail address: aldostefano.porcari@nhs.net (A. Porcari).