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Editorial

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The changing perspective on cardiac amyloidosis in the modern era

Gianfranco Sinagra, Aldostefano Porcari

Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI) and University of Trieste - Trieste, Trieste 34149, Italy.

Correspondence to: Prof. Gianfranco Sinagra, Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI) and University of Trieste – Via Valdoni 1, Trieste 34149, Italy. E-mail: gianfranco.sinagra@asugi.sanita.fvg.it

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INTRODUCTION

Recent years have witnessed a revolution in the traditional teachings and beliefs in cardiac amyloidosis (CA). In a very short time, this condition has gone from a rare, underdiagnosed, and difficult-to-diagnose disease with no specific treatment to being relatively prevalent, easy to diagnose, and treatable. This Special Issue on cardiac amyloidosis in *Vessel Plus* was conceived with the contribution of internationally recognized experts and opinion leaders in CA to provide updated, clinically relevant information for cardiologists and physicians of different specialties who are involved in the care of patients with amyloidosis as well as to discuss the many grey areas under investigation.

Amyloidosis: a history of failing biological systems

CA results from the extracellular deposition of misfolded proteins, mostly immunoglobulin light chain (AL) produced by an abnormal clonal proliferation of bone marrow plasma cells[1] and transthyretin (TTR) protein[2]. Age-related failure of homoeostatic mechanisms in wild-type TTR (wtTTR), destabilizing mutations in variant TTR (vTTR), or a hematological disorder in AL amyloidosis can prompt protein fibrillation[2]. Irrespective of the specific protein precursor, increased wall thickness, biatrial dilatation, and poor diastolic filling due to noncompliant ventricles are the hallmarks of CA[2,3], as discussed by De Gaspari *et al.*[4].

Cardiac amyloidosis: no more a needle in a haystack

In the contemporary era, CA has emerged as a relatively prevalent and underdiagnosed cause of heart failure (HF), associated with significant morbidity and mortality worldwide[2,5]. As underlined by Canepa *et al.*[6] on the changing disease prevalence, the exact epidemiological figures of CA are still under investigation. AL has traditionally been considered the most common form of systemic amyloidosis with recent data reporting an incidence of ≈ 1 per 100,000 individuals per year with cardiac involvement in half of the cases[2]. However, available estimates of CA prevalence and incidence are subject to referral bias, and longitudinal surveys (i.e., the Transthyretin Amyloidosis Outcomes Survey) suggest ATTR amyloidosis to be significantly more prevalent than previously thought[2,7]. CA, especially ATTR amyloidosis, was found to be more frequent in specific populations, e.g., 4% of subjects undergoing bilateral carpal tunnel surgery (CTS), 10% of patients with unexplained cardiac hypertrophy at the time of CTS[8], 13% of individuals hospitalized for HF with preserved ejection fraction, 5% of patients with hypertrophic cardiomyopathy, and 16% of patients with "paradoxical" low-flow low-gradient aortic stenosis[5].

A cutting-edge step forward for diagnosis was the possibility in achieving a non-invasive confirmation of ATTR-CA in the presence of high-grade cardiac retention (Perugini grade 2–3) in patients without monoclonal components (99% accuracy, 100% specificity)[9,10]. However, controversies and pitfalls of bone tracer scintigraphy exist, as critically pointed out by Mattana *et al.*[11]. Although this approach has increased the diagnostic yield and the chance of earlier disease recognition, a consistent diagnostic delay still remains (≈ 34 months from symptoms onset to diagnosis)[12]. In addition, the non-invasive algorithm suffers from some limitations in real-world applications, as in patients with intense cardiac retention at scintigraphy and monoclonal gammopathy of undetermined significance requiring histological evidence of amyloid deposits or in the presence of false-negative scintigraphy results due to peculiar TTR mutations (i.e., Phe84Leu and Ser97Tyr)[9,10]. In this scenario, cardiac magnetic resonance and positron emission tomography can aid clinicians in the diagnosis and management of the disease, as discussed by Pica *et al.*[13] and Genovesi *et al.*[14]. Awareness of the pros and cons of each diagnostic strategy in CA is gaining increasing importance in daily activity, especially in light of treatment and prognostic implications[15], as reviewed by Porcari *et al.*[16]. Furthermore, the presence of TTR mutations should be assessed in all patients with ATTR amyloidosis to distinguish between wtTTR and vTTR. The clinical translation of genetic testing in TTR amyloidosis with a focus on genotype–phenotype correlations and the management of asymptomatic carriers and familial screening was addressed by Scirpa *et al.*[17].

The unmet need for prognostic prediction in CA

Current prognostic stratification in AL- and ATTR-CA relies completely on scores integrating few specific biomarkers, but more clinical and instrumental parameters are emerging as relevant in the natural history of CA[17], as discussed by Camerini *et al.*[18] and Licordari *et al.*[19]. In this evolving scenario, the need for accurate prognostic stratification to guide identification of the best candidates to specific therapies emerges.

CA: a treatable disease

Treatment strategies for ATTR and AL amyloidosis have evolved significantly since orthotopic liver transplantation — the very first specific therapy for ATTR—was first performed in 1990[20]. Progress in knowledge about the "amyloidogenic cascade" has led to novel therapies including TTR stabilizers and TTR synthesis inhibitors for ATTR amyloidosis, chemotherapy and stem cell transplantation for AL amyloidosis, and cardiac transplantation for selected patients with advanced HF[20]. Tafamidis was demonstrated to reduce all-cause mortality and cardiovascular hospitalizations in the ATTR-ACT (Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy"), while Inotersen and Patisiran have been shown to drop hepatic TTR production by ≈ 80% in patients with vATTR amyloidosis with neuropathy[20]. As discussed by Di Nora *et al.*[21], AL-CA was previously considered a contraindication to heart transplant

because of concerns regarding worse long-term outcomes due to the amyloid involvement of other organs or the risk of recurrent amyloid in the graft[22]. However, the development of specific chemotherapy regimens enabling autologous stem cell transplantation has made long-term control of the plasma cell dyscrasia possible[22]. Therefore, timely diagnosis of CA is a critical issue to derive the largest treatment benefit.

Grey areas and future directions in amyloidosis

The availability of novel therapeutic strategies turning CA from an ominous to a treatable disease has provided new impulse towards research, but important issues still need to be addressed:

(1) Differentiate indolent "cardiac accumulation" associated with aging form CA, the authentic infiltrative disease.

(2) Understand the prevalence of AL and ATTR amyloidosis in various clinical settings.

(3) The clinical application of SPECT imaging should be done to increase the diagnostic accuracy of bone tracer scintigraphy and to quantify the amyloid burden in the heart.

(4) Define the minimal disease threshold to justify the initiation of novel treatments, particularly in light of their high costs and possible side effects.

(5) Define the criteria to identify patients with a so advanced CA that no significant benefit is expected from initiation of disease-modifying drugs.

(6) Identify the most appropriate tool to quantify the global amyloid burden and monitor its changes under specific treatment.

(7) Define baseline parameters to predict treatment response and orient clinical decision-making related to discontinuation of current drugs in favor of other medications or initiation on combination therapy.

A major reappraisal is underway concerning AL and ATTR amyloidosis in the modern era of *precision medicine,* and the collaboration among physicians of many specialties is essential to address evidence-based management of patients with this systemic disease.

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Authors' contributions

Contribute to the conception, outline and writing of the manuscript: Sinagra G, Porcari A

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Both authors declared that there are no conflicts of interest.

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