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Review Article

Current and future circulating biomarkers for cardiac amyloidosis

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Abstract

Cardiac amyloidosis (CA) comprises a heterogeneous group of medical conditions affecting the myocardium. It presents with proteinaceous infiltration with variable degrees of severity, prevalence and evolution. Despite this heterogeneity, erroneous protein folding is the common pathophysiologic process, yielding the formation of a single misfolded protein (monomer) that progressively evolves and ultimately forms amyloid fibers. Additionally, by seeding out from the organs of origin, intermediates called oligomers metastasize and restart the process. Such self-echoing behavior makes the secondary affected organs as important as the primary ones. Unfortunately, CA can be clinically challenging and only suggestive in a late stage of its natural history, leaving a narrow therapeutic time window available. In light of the evolutionary nature of amyloidosis, here, we propose a new classification of the currently used biomarkers based on time stages with different specificity and applicability across CA subtypes. Early markers (free light chains, serum amyloid A, β_2-microglobulin, osteopontin and osteoprotegerin) can be employed for disease detection. Intermediate markers [soluble suppression of tumorigenicity 2 (sST-2), midregional proadrenomedullin (MR-proADM), von Willebrand factor (vWF), hepatocyte growth factor (HGF), matrix metalloproteinases (MMPs) and tissue inhibitor metalloproteinases (TIMPs)] can provide information on the biological mechanisms of myocardial damage. As in heart failure, late-stage biomarkers (troponins and natriuretic peptides) can help clinicians with prognosis and therapeutic response evaluation in CA. Such findings have generated a remarkable foundation for our current knowledge on CA. Nevertheless, we envision a future class of biomarkers targeted at upstream events capable of detecting folding defects, which will ultimately expand the therapeutic window.

Keywords: cardiac amyloidosis; biomarkers; protein misfolding; myocardial damage

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Introduction

Amyloidosis is a medical condition characterized by the build-up of proteinaceous byproducts, traditionally within the extracellular space, yielding histological alterations and organ dysfunction[1]. It can be classified as localized or systemic based on its anatomical distribution. At present, nearly forty different human proteins can lead to relevant forms of amyloidosis, eight of which are capable of affecting the heart with variable incidences and severity[2, 3]. In addition to these forms, the detection of intracellular aggregates[4], together with findings of myocardial involvement by additional peptides of cardiac and extracardiac origins, complicates the overall portrait of amyloidosis and necessitates future classification updates[5].

Independently of the biological precursor and origin, all types of amyloidosis stem from a common pathogenic mechanism: an erroneous protein folding process, namely, "misfolding"[6]. A neosynthesized aminoacidic sequence is obligated to undergo the folding process in order to acquire its correct spatial conformation, which will dictate its physiological role, localization, interaction, and turnover[7]. A series of adverse events (genetic mutations, increased synthesis, iatrogenic factors, inefficient quality control, aging and the propensity of the protein per se) can alter this process in up to one-third of all synthesized proteins[8, 9].

Once an erroneously arranged protein (namely, a monomer) is generated and has overwhelmed protein quality control systems[10], it starts aggregating into larger and more complex structures, such as pre-amyloid oligomers (PAO hereafter). Such a peculiar, abnormal and cytotoxic structure self-sustains its own accumulation and can travel and deposit in distant and vulnerable districts in a metastatic-like manner[11, 12]. Over time, PAO grow in size and yield more stable structures, such as linear and circular protofibrils and ultimately, amyloid

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fibers. These pathognomonic structures of β-plated sheets are mostly composed of protein bundles arranged in an ordered array from 7.5 to 10 nm in diameter of rigid, linear and non-branching fibers[13, 14]. Such unique physico-chemical features determine distinctive tinctorial properties, allowing investigators to identify amyloidosis and confirm a diagnostic hypothesis. While endomyocardial specimen positivity remains the current diagnostic gold standard, a less invasive diagnostic procedure, such as abdominal fat pad fine needle aspiration, has reached comparable results only in cases of massive amyloid infiltration[15]. Similarly, smaller and/or intracellular deposits[4] might be detected only with expensive and non-routine methods, such as electron microscopy.

Despite our better understanding of these mechanisms, which has been refined over the last few decades, unfortunately, amyloidosis is clinically suggestive only in a late stage of its natural history, and it might be undiagnosed in cases with subtle and non-specific signs or symptoms, gaining the moniker of "the great pretender"[16]. On the other hand, non-traditional amyloidosis has been clinically undetected for long time.

Extensive descriptions of major cardiac amyloidosis (CA) subtypes are reported elsewhere[17]. In this review, we are offer a glimpse into the current state of knowledge of this disease to better understand its associated biomarkers.

Major known subtypes of cardiac amyloidosis

The subgroups herein reported are summarized in Table 1. For a more extensive description of a greater number of kinds of CA, we suggest the cited review[18].

Light chain amyloidosis (AL)

All subjects with AL suffer from a form of cell dyscrasia. Cardiac involvement prevalence is approximately 50% depending on the kind of hematologic disorder (*eg*, lymphomas, MGUS, or multiple myeloma). The mean age of diagnosis is within the seventh decade of life, and men are frequently more affected than women. Between light chains, λ represents the causative precursor in nearly 80% of cases compared to κ, suggesting a higher propensity of the former isotype to misfold[19]. Among systemic manifestations, periorbital and peribuccal purpura, together with macroglossia, are highly indicative of

Table 1. Main biological, demographic and clinical features of major subtypes of cardiac amyloidosis.

Type of cardiac amyloidosis	AL	SFA (mutTTR)	SSA (wtTTR)	AA	IAA	$A\beta_2M$
Biological precursors (protein)	Light chain immunoglobulins (70% λ, 30% κ)	Mutated transthyretin	Wild-type transthyretin	Serum amyloid A	Atrial natriuretic peptide	β_2- microglobulin
Precursor origin	B cells	Liver	Liver	Liver	Heart	All nucleated cells + Iatrogenic
Associated conditions	Cell dyscrasias (MM, NHL, MGUS)	Related to the type of mutation	Associated with aging	Persistent inflammatory conditions	Heart failure	Prolonged hemodialysis treatments
Prevalence of cardiac involvement	50% *(depending on cell dyscrasia)*	Highest prevalence in V122I, V30M, T60A mutations	8% to 16% in patients >80 years	1% to 15%	15%	35% *(after 10 years of treatment)*
Reported mean age at presentation	60 years	>40 years 52 years (*depending on mutations)*	76 years	50–58 years	70 years	*Variable (after 10 years of treatment)*
Majorly involved organs	Kidney, liver, heart	Peripheral/ autonomic nerves, heart	Kidney	Thyroid, spleen, gastrointestinal kidney, liver	n/a	Kidney, heart, gastrointestinal tract
Cardiac findings						
LV wall thickening	+ (15 mm)	+ (16 mm)	++ (19 mm)	-	-	+
ECG low voltage	++ (60%–71%)	+ (25%)	+ (40%)	+ (17%)		
Pseudoischemic	++ (48%–63%)	+ (42%)	+ (40%)	+ (17%)		
LVEF%	suboptimal	suboptimal	suboptimal low	n/a	suboptimal	low
Diastolic dysfunction	++	+	+			
Associated CV signs			Atrial fibrillation	Hypertension	Atrial fibrillation, hypertension	
Mortality	Mean survival from HF presentation 6 months		35% at 5 years from bioptic diagnosis	31% at 10 years with cardiac involvement		

AL; moreover, heart failure represents the worst prognostic factor.

Systemic senile amyloidosis (SSA) with wild-type transthyretin (wtTTR)

Transthyretin is a carrier protein mainly synthesized in the liver. The tertiary structure of wild-type transthyretin (wtTTR) is a determinant itself for protein misfolding, even in the absence of a mutation. A recent prospective cohort study extensively described the demographic, laboratory and cardiac morphofunctional features of this population[20]. This type of CA is of critical importance since the median survival from presentation is 4.6 years, and the median age at death is 78, posing a real challenge for the medical and scientific community as a threat to the elderly population.

Systemic familial amyloidosis (SFA) with mutated transthyretin (mutTTR)

More than 100 different mutations of TTR are known to date[21]. The clinical portrait and organ involvement greatly vary across mutations. In fact, neurological and cardiovascular involvement can be either present jointly or separately with different degrees of severity presenting at different age ranges[22, 23]. Etiological treatment is liver transplant, and overall survival at 4-year follow-up from presentation ranges from 79% to 16% for V30M and V122I mutations, respectively.

Amyloid A amyloidosis (AA)

This kind of amyloidosis can occur in chronic inflammatory diseases, persistent sepsis, or periodic fever syndromes, and its biological precursor is an acute phase reactant predominantly synthesized by the liver called serum amyloid A (SAA)[24]. The kidneys are frequently affected, possibly explaining the arterial hypertension commonly observed in this class of patients. CA is a rare finding, and its prevalence has been reported within 1%-15% of patients in two different studies[25, 26]. The median survival from diagnosis is 11 years.

Isolated atrial amyloidosis (IAA)

Among proteins, atrial natriuretic peptide (ANP) is also prone to misfold. In fact, it can lead to a peculiar form of CA restricted to the atrial chambers. This histological alteration constitutes the anatomical substrate for electrical disturbance and atrial fibrillation onset[27].

β_2-microglobulin amyloidosis (Aβ_2M)

An iatrogenic form of CA can be observed in patients undergoing hemodialysis. Reports document an occurrence after a decade of dialytic treatment due to the concentration of β_2-microglobulin, a type 1 major histocompatibility complex (MHC I) subunit[28]. A long-standing hemoconcentration and homology with light chains immunoglobulins[29] represent two concomitant causes of amyloid formation in these patients[30].

Newly recognized cardiac amyloidoses

This heterogenous group is composed of newly identified forms of CA with non-mutually exclusive features, such as atypical histological presentation (intracellular aggregates) associated with additional cardiac dysfunction, originating either by cardiac or extracardiac biological precursors. Both desmin[31, 32] and cofilin[33], which belong to the cardiomyocyte cytoskeleton apparatus, were found in intracellular aggregates in the context of dilated cardiomyopathy. In addition, the recent detection of Aβ in the human myocardium adds a novel piece to the complex biological jigsaw of Alzheimer's disease, supporting the hypothesis of Alzheimer's disease as a systemic or metastatic disease[34].

Methods

We searched the PubMed library (last accessed on October 1, 2017) for articles in English with full text available and reference lists of related papers. The terms employed in the query were "cardiac amyloidosis biomarkers" and "heart amyloid biomarkers", either alone or together in different combinations.

Biomarkers

In light of these remarkable differences among subtypes of amyloidosis, it is intuitive that a single biomarker cannot carry universal predictive power. Nevertheless, over the past years, a significant body of literature has been produced with the intention of exploring and testing a series of biomarkers for early disease detection, risk stratification, patient prognosis, and therapy monitoring. As correctly set out by Morrow and de Lemos, a clinically applicable biomarker should fulfill three criteria: accuracy, informativeness, and superiority over other available tests[35].

Given the evolutionary nature of amyloidosis, biomarkers can be classified depending on the stage of the disease: monomer formation, oligomeric evolution and amyloid fiber accumulation. These subclasses can be employed for different levels of prevention (from primary to tertiary). In fact, they can be respectively employed for assessing risk stratification for future amyloid occurrence, early disease detection and prognosis evaluation in cases of cardiac involvement, as shown in Figure 1. This proposed classification oversimplifies amyloidogenic processes; however, it might help clinicians manage subjects at risk and affected patients over time. Despite of a lack of biomarkers for the newly discovered subtypes and the low specificity in detecting the origin of production, future biomarkers could be included and classified on the basis of their prediction to pinpoint the exact biochemical abnormality in CA natural history. Table 2 offers a general overview of currently available knowledge on biomarkers tested in amyloidosis by CA subtype.

Biomarker classes

Due to the amount of literature available and to facilitate a rapid understanding, we start by evaluating and discussing late-stage biomarkers and proceed backwards to early-stage ones because they have a lower number of findings available at present.

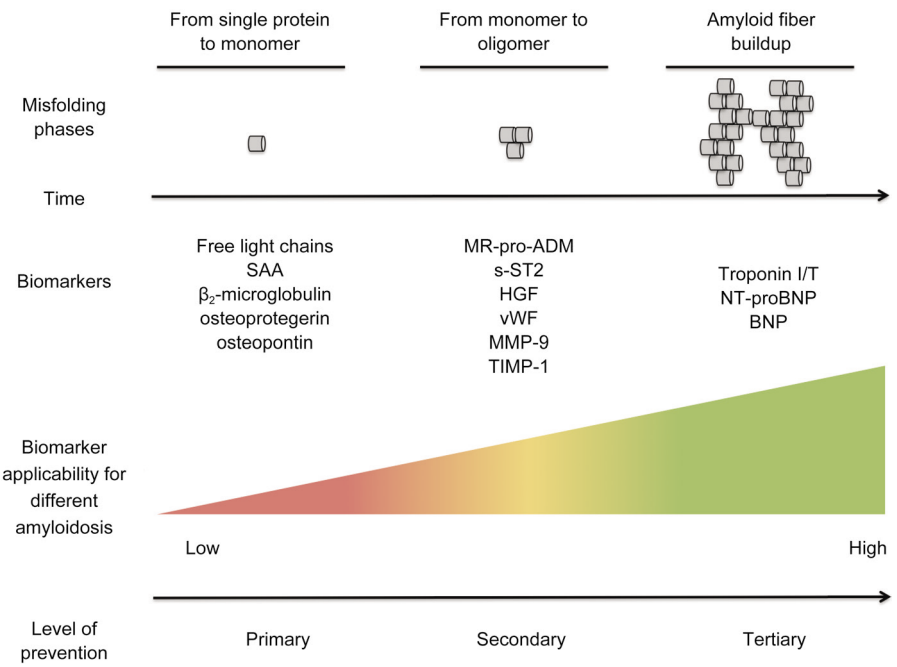

Figure 1. Putative amyloidosis phases for classification of biomarkers classes in cardiac amyloidosis.

Late-stage biomarkers for cardiac amyloidosis

Amyloidosis is frequently diagnosed at a late timepoint when the myocardium is already infiltrated by amyloid fibers. At this stage, traditional cardiac involvement is easily detectable with different methods: imaging, histological and clinical assessment. In this phase, cardiac impairment is characterized by preserved/suboptimal systolic function and reduced degree of relaxation, which is consistent with the clinical definition of heart failure with preserved ejection fraction (HFpEF)[36]. For this reason, the vast majority of biomarkers in CA are the ones also employed in case of heart failure of different etiologies. Therefore, at this step, circulating biomarkers are not generally specific to CA, and unfortunately, the lack of specific late stage biomarkers has also contributed to the delayed recognition of other forms of cardiomyopathy with newly recognized amyloid deposition. Nevertheless, this lack of specificity enables broader application across all subtypes (AL, SFA, SSA, AA, *etc*). These biomarkers, together with the intermediate stage ones, provide information related to established molecular and cellular dysfunctions occurring in heart failure: myocyte apoptosis (cardiac troponins), increased fibrotic deposition, sustained inflammation and abnormal myocardial stretch-

Table 2. Representative overview of biomarkers tested and employed in different cardiac amyloidosis subclasses.

	Cardiac amyloidosis subtypes					
	AL	SFA (mutTTR)	SSA (wtTTR)	AA	$Aβ_2M$	Aβ
(hs)cTnI	•		•			
(hs)cTnT	•	•	•			
BNP	•		•			
NT-proBNP	•	•	•			
sST2	•					
MR-proADM	•					
vWF	•					
HGF	•					
MMP-9	•		•			
TIMP-1	•		•			
FLC	•					
SAA				•		
$β_2$-Microglobulin					•	
OPG	•					
OPN	•					

ing[37, 38]. In the presence of persistent oxidative, inflammatory and abnormal stretching stresses, cardiac troponin I (cTnI) and cardiac troponin T (cTnT) would be released and be detectable in the bloodstream[39-42].

At present, these cardiac biomarkers are globally accepted as prognostic tools for hard clinical endpoints in different subclasses of amyloidosis (AL, SFA, and SSA). Markers of myocardial damage, such as cTnI and cTnT[43], together with cardiac responsiveness peptides BNP and NT-pro-BNP (or even their combined association), have shown high predictive power[44]. In recent years, high sensitivity cardiac troponin T (hscTnT) has replaced previous generations assays, and it has set a novel gold-standard, particularly in AL. In fact, hscTnT values above 50-54 ng/L are indicative of increased mortality rates[45] and strongly correlate with NYHA functional class, LVEF, and left ventricular wall thickness[46]. As documented by Palladini for the first time, natriuretic peptides are applied in CA prognosis[47]. As far as NT-proBNP is concerned, a recent study has proposed different cut-off values by ROC analysis for overall survival in AL and SSA, which are 2480 pg/mL and 3470 pg/mL, respectively[48]. According to Ishiguro and colleagues, a cut-off value of 200 pg/mL for BNP is significant for the prediction of survival in the AL population[49]. In the setting of CA with cardiac onset, this class of markers might provide information regarding cardiac involvement and the degree of dysfunction both at single cell and organ levels.

Mid-stage biomarkers for cardiac amyloidosis

Cell vulnerability and death in CA can be linked to sustained local inflammation occurring as a consequence of fiber accumulation or more likely, the presence of PAOs, which are now believed to be the most prominent driving force in protein misfolding related diseases[50]. Effectors or sensors of damage, especially inflammation, have been borrowed from other cardiac diseases and tested in this field, where AL represents the most frequent subpopulation analyzed for this matter.

Soluble suppression of tumorigenicity 2 (sST2), an IL-33 decoy receptor, has been proven to be an independent powerful marker of prognosis in AL[51]. By binding to IL-33, it lowers the cardioprotective effect against fibrosis, contractility and hypertrophy of its ligand[52]. A cut-off value of 30 ng/mL has been established. The 1- and 5-year survival rates of subjects with ≥30 ng/mL were 43% and 22%, respectively, and the 1- and 5-year survival rates of subjects with lower levels of sST2 were 81% and 52%, respectively.

An additional marker of inflammation that is not restricted to myocardial tissue is midregional proadrenomedullin (MR-proADM). The human *ADM* gene encodes a pre-pro-hormone that is subsequently cleaved, generating three distinct vasoactive peptides: adrenomedullin, adrenotensin and proadrenomedullin. Along with these peptides, a fourth seemingly inactive peptide (MR-proADM) is released[53]. Despite its apparent inertness, it is ubiquitously expressed at high levels in various districts, such as bone, adrenal cortex, kidney, blood vessels, heart, adipose tissue and anterior pituitary, and it is likely related to vascular permeability and inflammation, thereby representing a predictor of early outcomes in acute settings[54, 55]. Values above 0.75 nmol/L predicted an increased mortality risk (HR=3.8); nevertheless, it lacks an association with amyloid infiltration, which suggests that MR-proADM has a role in adverse systemic responses in AL[56].

As anticipated, in addition to cardiomyocyte death, endothelial loss should be investigated. von Willebrand Factor (vWF) was evaluated as an additional marker of vascular damage. Values above 230 UI/dL were associated with poor prognosis independently of the clinical stage of AL patients[57].

Interestingly, hepatocyte growth factor (HGF) was significantly higher in AL than in other cardiac maladies (HF, LVH, or SSA without cardiac involvement) and was slightly increased in SSA with cardiac infiltration. A cut-off value of 622 pg/mL for HGF generated two cohorts with the most divergent results in terms of survival estimates at 5-year follow-up, which were 70% *vs* 30% for values below and above the median, respectively[58]. The significance of increased HGF must be elucidated: the authors have hypothesized a putative angiogenic role of HGF in response to amyloid deposition in vessels. Nevertheless, endothelial mesenchymal transition (EMT) could represent an additional or alternative mechanism of action, ultimately leading to cardiac dysfunction as high HGF concentrations shift the myocardium towards fibrotic changes[59]. Despite being a simple speculation, this intriguing hypothesis should be carefully tested in the setting of human CA in the future[60].

Finally, extracellular matrix (ECM) remodeling has been evaluated in the plethora of pathological events occurring with CA, sustaining abnormal collagenolytic activity in the human myocardium. A coupled increase of serum matrix metalloproteinases-9 (MMP-9) together with tissue inhibitor metalloproteinases-1 (TIMP-1) was detected in AL amyloidosis only. This finding is suggestive of either a peculiar toxic signature of light chains in cardiac ECM compared to transthyretin or is associated with an accelerated amyloidogenic process like what occurs in AL[61]. As far as this class is concerned, this group of biomarkers can detect initial molecular abnormalities and describe a biological footprint occurring in amyloidogenic processes regardless the organ of origin. This kind of information can discriminate between the different etiologies of HF and therefore stratify patients based on the effective mechanism of damage.

Early stage biomarkers for cardiac amyloidosis

In AL, serum-free light chains (FLC) λ (normal range 0.57–2.63 mg/dL) or κ (0.33–1.94 mg/dL) are elevated; therefore, levels outside the physiological kappa/lambda ratio range (0.26 to 1.65) are suggestive of abnormal clonal expansion (<0.26 clonal λ; >1.65 clonal κ overproduction)[62]. In addition, FLC values are quantitatively evaluated as they carry a prognostic value either alone or in association with other parameters. FLC values above an indicative range of 152–196 mg/L correlated with septal wall thickening, increased TnT, and the involvement of a higher number of organs, constituting a reli-

able predictor of mortality in an observed cohort of AL[63] and in patients undergoing stem cell transplantation[64]. With the same intention, a composite model was conceived by employing two additional markers (BNP/NT-proBNP + TnT) in association with FLC and by assigning a score of 1 for each marker with a level above the cut-off value. In this manner, four different stages (I to IV) were generated; the survival rates at 5-year follow-up for stages I, II, III, and IV were 68%, 60%, 27% and 14%, respectively[65].

Concerning AL, bone remodeling represents a local critical event in the natural history of cell dyscrasias, and osteopontin (OPN) and osteoprotegerin (OPG) have found applications in CA evaluation. The former is highly expressed in osteoblasts and osteoclasts, although OPN modulations are observed in various cardiac pathological conditions, particularly in myocytes[66]. The latter is a tumor necrosis factor (TNF) family member, and it acts as a decoy receptor for the receptor activator of nuclear factor κB ligand (RANKL), configuring as an inhibitor of osteoclastogenesis. Nevertheless, its expression is not limited to the bone marrow as endothelial and smooth muscle cells express abundant levels, suggesting pleiotropic effects, especially in inflammation[67]. Kristen and colleagues found that OPN is associated with worse NYHA functional class and morphofunctional parameters[68]. The authors set a cut-off value of 426.8 ng/mL for predicting overall mortality. As far as OPG is concerned, Kastritis employed this biomarker to distinguish AL compared to controls or hematological malignancies without cardiac involvement. OPG was significantly higher in cases of cardiac involvement and was directly correlated with NT-proBNP, predicting overall survival. Such features suggest the broader applicability of OPN and OPG beyond CA, such as in atherosclerosis and HF, and requires future studies for a deeper understanding of their effective role[69].

In AA, the biological precursor of PAOs, namely, SAA, represents the most powerful predictor of overall mortality as its increase is highly correlated with relative death risk[25]. Of note, being an established acute-phase marker of inflammation and predictor of mortality in coronary artery disease, it should not be considered to be a sole marker for CA[70].

Finally, β_2-microglobulin was found to be increased in a series of patients with amyloidosis presented by Gertz nearly 30 years ago, and it was identified as an independent predictor of mortality in patients with or without HF; a value above 2.7 mg/L was an indicator of poor prognosis[71].

As for mutated transthyretin, a genetic test should be considered in the diagnostic algorithm even in the case of a negative family history of amyloidosis. Such a test provides additional information to proteomic assays and allows an early diagnosis for anticipated liver transplantation before the amyloid load overwhelms cardiac resistance and function[72].

Directions for future biomarkers

With larger cohorts and higher numbers of parameters, future studies will likely revise the cut-off values over-time. Nevertheless, future investigations should aim at identifying novel biomarkers and creating an updated scoring system with higher predictive values than the present ones.

Predicting patients' response to therapy or regimen efficacy represents an additional expanding field of interest in biomarker research. At present, this specific application is limited to few subclasses of CA because liver transplant and chemotherapy are the only etiological treatments against SFA and AL, respectively. As recently evaluated by Sperry and colleagues, a triple combined therapy (bortezomib, dexamethasone, and an alkylating agent) appears to be superior to other treatments with a survival rate of approximately 60% *vs* 30% at 2-year follow-up[73]. In this study, FLC was the only covariate capable of increasing the survival predictability of a model upon adjustment.

As Palladini correctly noted, multiple organ dysfunctions are observed in amyloidosis, and renal impairment is not an uncommon finding, especially in AL. For this reason, biomarkers will have to be adjusted for glomerular filtration rate as renal dysfunction can alter their clearance, requiring corrected cut-off values[74].

Concerning scoring systems, the association of established bone remodeling markers (RANKL, osteocalcin, bone-alkaline phosphatase, C-terminal and N-terminal telopeptide, and tartarate-resistant acid phosphatase) together with ones discovered in the future might lead to informative results, allowing clinicians to better predict hematologic malignancy evolutions, stage them on a timely basis and estimate the likelihood of cardiac infiltration.

In the absence of specific biomarkers targeted to precursor proteins, an emerging class under consideration is the one related to PAO synthesis and accumulation with PAO. Their specificity for PAO and related pathogenic mechanisms currently limit their applicability to diagnose amyloid subtypes. Nevertheless, they appear to be easily detectable, etiology-targeted markers, allowing clinicians to identify the disease at an early stage prior to systemic progression. This feature is pivotal in amyloidosis if we consider the long lag phase of biological burden compared to the short time-window between cardiac manifestation and death (6 months in AL and 5 years in SSA), especially when etiological therapies are scarce or even unavailable. Importantly, given their role in cell toxicity, the detection of PAO may prove instrumental in defining active disease states from stable disease or disease in remission in both traditional and non-traditional amyloidoses.

Conclusions

Over the last decades, medical research has focused its attention on amyloidosis, generating a remarkable amount of literature on this subject. This scientific production has shed light on the underestimated aspects of this pathological process, and it will constitute a solid foundation for future studies in this expanding field of medical research.

Despite this growing knowledge, a winning strategy for amyloidosis treatment would shift our attention to the molecular processes governing the early stage of the disease. A critical development in the generation of new biomarkers

would be tailoring the detection of misfolding occurrence and PAO accumulation, which would lead to interesting results. The wishful aim of early detection with respect to myocardial thickness and therefore the natural history of CA, must be pursued as it will have two major consequences. First, detecting CA before ventricle thickening and excessive amyloid load will significantly expand the therapeutic time-window at our disposal since HF remains as the worst prognostic factor[75, 76]. Second, a better comprehension of this disease will guide us towards effectively designing and introducing etiological therapies, tackling misfolding itself.

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Abbreviations

Aβ_2M, β_2-microglobulin amyloidosis; AA, amyloid A amyloidosis; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CA, cardiac amyloidosis; cTnI/T, cardiac troponin I/T; ECM, extracellular matrix; EMT, endothelial mesenchymal transition; FLC, free light chain; HF, heart failure; hscTnI/T, high sensitivity cardiac troponin I/T; HGF, hepatocyte growth factor; IAA, isolated atrial amyloidosis; LVEF, left ventricle ejection fraction; MGUS, monoclonal gammopathy of undetermined significance; MR-proADM, mid-regional proadrenomedullin; NT-proBNP, N-terminal pro brain natriuretic peptide; OPG, osteoprotegerin; OPN, osteopontin; PAO, preamyloid oligomer; RANKL, receptor activator of nuclear factor kappa-B ligand; SAA, serum amyloid A; SFA, systemic familial amyloidosis; SSA, systemic senile amyloidosis; sST2, soluble suppression of tumorigenicity 2; TNF, tumor necrosis factor; vWF, von Willebrand factor.

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