nature reviews cardiology

https://doi.org/10.1038/s41569-026-01359-8

Review article

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Cardiac and vascular involvement in protein misfolding diseases

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Abstract

Protein misfolding diseases impose a substantial and often under-recognized burden on both the heart and vasculature. In this Review, we outline how the failure of proteostasis drives oligomer toxicity, amyloid deposition and inflammation in cardiovascular tissues as well as microvascular injury and thrombosis, which culminate in cardiovascular dysfunction. We define the cardiovascular hallmarks of protein misfolding diseases, focusing on transthyretin amyloidosis and immunoglobulin light chain amyloidosis, and the disease-specific organ tropisms. We examine neurodegenerative proteinopathies affecting the heart–vascular–brain axis, highlighting how amyloid-β and α-synuclein accumulation contribute to dysautonomia, vascular dysfunction and adverse outcomes. We summarize diagnostic pathways and clinical indicators for early diagnosis of cardiovascular involvement in protein misfolding diseases and review established and emerging biomarkers of vascular stress and proteotoxic load. We also map the current therapeutic landscape for protein misfolding diseases, including strategies to reduce the synthesis of precursor proteins or promote the stabilization of mature proteins as well as fibril-directed therapies, and discuss remaining challenges, such as residual cardiovascular risk, that support the development of mechanism-informed therapeutic approaches. Finally, we propose a research roadmap that prioritizes systematic cardiovascular screening in at-risk populations, harmonized methods for vascular phenotyping, biomarker-anchored mechanistic clinical trials across protein misfolding diseases, and artificial intelligence-based approaches and precision medicine frameworks that integrate genotype or distinct protein conformational strain patterns, organ tropism and dynamic proteostasis measures.

Sections

Introduction

Mechanisms

Presentation, diagnosis and prognosis

Treatment and management

Challenges and future directions

Conclusions

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Key points

- Protein misfolding diseases are systemic disorders that share pathways of proteotoxic stress, inflammation, vascular dysfunction and organ injury.
- In-depth understanding of the pathophysiology of protein misfolding diseases opens opportunities for shared methodologies to develop novel biomarkers and therapeutic strategies, accelerating early disease recognition and precision treatment.
- Cardiovascular involvement in protein misfolding diseases is the main determinant of morbidity and mortality in these patients, which has led to intense research on novel therapeutic targets and the development of new therapies.
- Immunoglobulin light chain amyloidosis and transthyretin amyloidosis are prototypical cardiovascular proteinopathies, whereas amyloid-β and medin are amyloidogenic precursors contributing to heart–kidney–vascular–brain axis dysfunction and vascular pathologies, respectively.
- Systematic screening for protein misfolding diseases in the general population, using artificial intelligence-based tools, and in at-risk subpopulations, using multimodal monitoring with advanced imaging, biomarkers and artificial intelligence-based tools, could improve patient outcomes.
- Disease-modifying therapies improve outcomes in patients with immunoglobulin light chain amyloidosis or transthyretin amyloidosis, but clinically meaningful residual cardiovascular risk remains.

Introduction

Protein misfolding diseases (PMDs) comprise a heterogeneous group of conditions characterized by the accumulation of non-native, unfolded or misfolded proteins that cause cell death, disrupt tissue architecture and impair organ function (Fig. 1). Although PMDs were initially linked mainly to neurodegenerative disorders, many also affect the cardiovascular system[1] (Fig. 2 and Table 1). Misfolded protein aggregates, arising from an imbalance between protein synthesis or folding load and protein quality control and clearance capacity, are key drivers of cardiovascular dysfunction and contribute substantially to morbidity and mortality globally[1].

Owing to the limited regenerative capacity of cardiomyocytes and their finely tuned structural and functional homeostasis, as well as their high metabolic demands, the heart is particularly susceptible to proteotoxic stress. Misfolded proteins that accumulate in myocardial and vascular tissues can drive the formation of amyloid fibrils (ordered, insoluble protein aggregates) and, in certain cases, inflammation, leading to fibrosis, which can culminate in organ failure[2,3]. With chronic disease and advancing age, protein quality control wanes, impairing proteostasis and causing aggregate formation and tissue damage, thereby accelerating initiation and clinical progression of disease[4,5]. Despite therapeutic advances, including protein stabilizers, mRNA silencers and immunotherapies, a substantial residual cardiovascular risk persists (including arrhythmias, progression of existing heart failure and cardiovascular-related death) in patients with PMD, supporting the need for new mechanism-based interventions.

In this Review, we first delineate the hallmarks of cardiac and vascular involvement in PMDs. We focus mainly on transthyretin amyloidosis (ATTR) and immunoglobulin light chain (IgLC) amyloidosis (AL amyloidosis), whereas α-synucleinopathies and amyloid-β-related diseases are discussed primarily to support a unifying framework of cardiovascular proteotoxicity. We provide a comprehensive overview of clinical phenotypes, describe shared and disease-specific molecular signatures, and examine the evolving landscape of diagnostic and prognostic biomarkers. We also evaluate current and emerging therapies and explore opportunities for mechanistically grounded precision medicine. Evidence on cardiovascular involvement across PMDs is uneven; mechanistic insights largely derive from experimental systems, and clinical evidence is often observational, referral-based and enriched in some disease stages. Accordingly, we distinguish between plausibility based on experimental data, human association and outcomes data, and genetically informed evidence supporting causality, and we highlight possible biases (confounding, reverse causality and disease-stage selection) when interpreting vascular phenotypes and proposing therapeutic strategies. By integrating clinical and experimental insights, we propose a framework that positions protein misfolding as a central pathophysiological process in both rare and common PMDs, contributing to cardiovascular disease (CVD).

Mechanisms

PMDs converge on a handful of cellular and molecular processes that impose persistent stress on the myocardium and the vasculature, including proteostasis collapse, oligomer toxicity, fibril deposition, oxidative stress, inflammation and thrombosis (Fig. 1). However, these diseases diverge in site of origin, the type of precursor of protein aggregation and, crucially, the position on the protein aggregation pathway of the causal amyloids, the biophysical properties and tissue tropism of the fibrils, and the different fibril structural conformations (known as strains) that modulate organ involvement and clinical phenotype. ATTR is characterized by slow amyloid infiltration into myocardial and valvular tissues, leading to restrictive cardiomyopathy[6]. AL amyloidosis is characterized by aggressive oligomer toxicity causing rapid development of heart failure and multiorgan dysfunction[7]. In amyloid-β-related diseases, vascular deposition, inflammation and platelet activation drive atherothrombosis[8]. In medin vascular proteopathy, medin amyloids produce in situ proteotoxic effects that lead to arterial stiffening, arterial wall degeneration and cross-seeding of other amyloids[9]. Accumulation of misfolded α-synuclein is linked mainly to neurogenic dysregulation of cardiac and vascular function with dysautonomia[10].

The distinction between primary vasculopathies and vascular involvement secondary to systemic amyloidosis is crucial for guiding mechanistic thinking and research priorities. In the classical systemic amyloidoses, such as AL amyloidosis and ATTR, vascular damage is secondary; the amyloidogenic precursor is produced remotely (in the bone marrow in AL amyloidosis and the liver in ATTR), circulates systemically and then deposits in the vessel wall as part of a broader pattern of organ infiltration[7,11–14]. The kinetics of aggregation are governed primarily by the concentration and stability of the circulating amyloidogenic precursor, and the vasculature is one of several target tissues[7,11]. Medin vascular proteopathy represents a fundamentally different situation. The precursor protein lactadherin (also known as MFGE8) is produced locally in the vasculature by vascular smooth muscle cells and pericytes, and the protein aggregation process, from initial misfolding

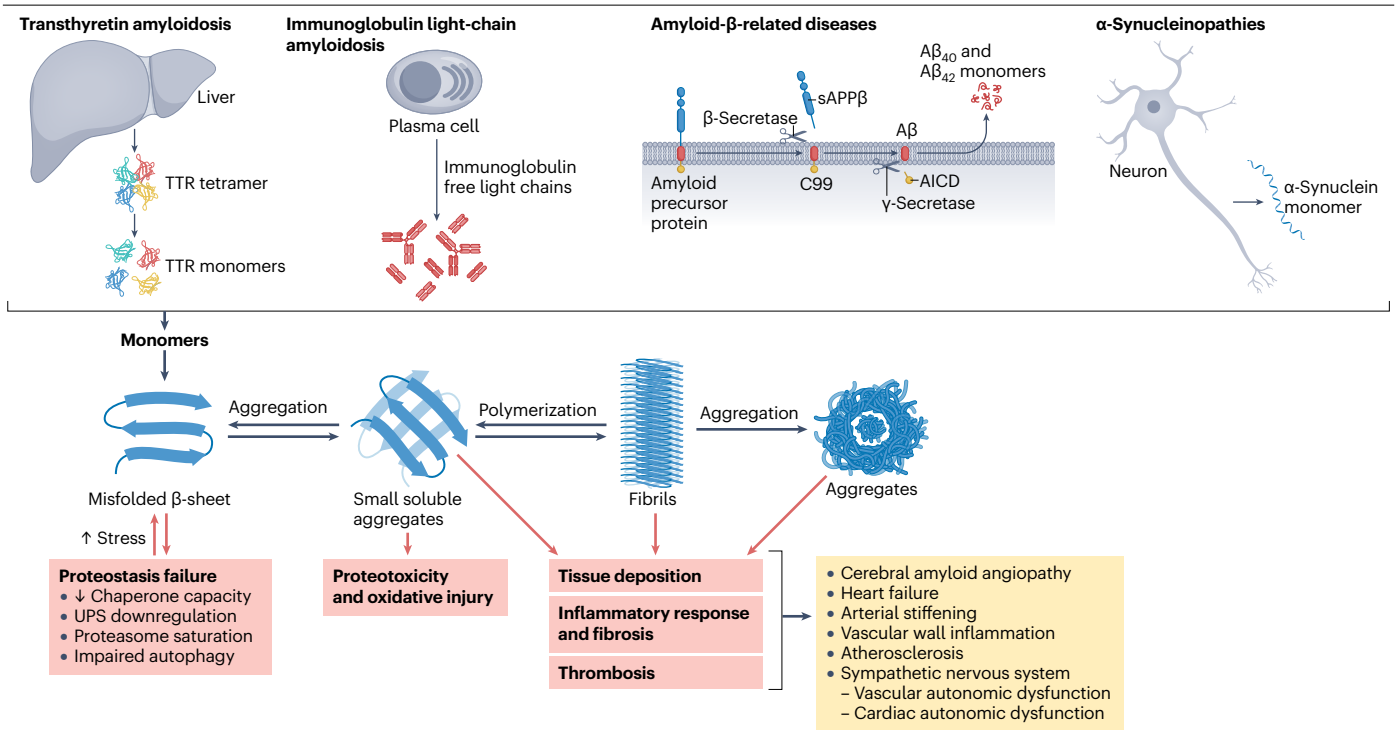


Fig. 1 | Shared pathophysiological pathways in protein misfolding diseases. Protein misfolding diseases comprise a heterogeneous group of conditions characterized by the accumulation of misfolded proteins that disrupt tissue architecture and eventually impair organ function. Monomers of transthyretin (TTR), immunoglobulin light chains, amyloid-β_{40} ($A\beta_{40}$) and $A\beta_{42}$, and α-synuclein can misfold into a β-sheet conformation in certain pathophysiological conditions (such as failure of proteostasis) and in aged tissues or organs, and can subsequently aggregate, forming oligomers, fibrils and larger aggregates. Shared pathological pathways across the proteinopathies shown in the figure can lead to cardiovascular cellular and tissue alterations (proteostasis collapse, oligomer toxicity, fibril deposition, oxidative stress, inflammation and thrombosis) that impose persistent stress on the myocardium and vasculature. These shared pathological mechanisms activated by misfolded proteins result in tissue damage and organ failure. AICD, amyloid precursor protein intracellular domain; C99, 99-amino acid C-terminal fragment; sAPPβ, soluble amyloid precursor protein β; UPS, ubiquitin–proteasome system.

through to nucleation to fibril deposition, occurs entirely within the vessel wall[9,15]. This disease is a primary vascular proteopathy in the strict sense because the proteotoxic insult originates in situ and the pathological consequences arise from local aggregate accumulation rather than from systemic overload of precursor proteins[9,16]. However, the boundary between systemic amyloidoses and primary vasculopathies is not always sharp. Some systemic amyloidoses involve local vascular proteotoxicity, and medin itself can interact with systemically derived amyloids such as amyloid-β and transthyretin amyloid. Importantly, the conversion of soluble protein into aggregated, β-sheet-rich assemblies can be initiated through various routes, with implications for diagnosis, biomarker development and therapeutic targeting.

Disruption of proteostasis

The cellular proteome is highly complex and dynamic, reflecting the continuous adaptation of the transcriptome to physiological and environmental challenges. Together with the secretome, the proteome is constantly curated by the proteostasis network, a multicomponent ensemble of protein machineries distributed across all cellular compartments and the extracellular space, and tightly regulated by cell-autonomous and non-autonomous pathways[17,18] (Fig. 3 and Box 1).

Protein folding is the progressive organization of partially folded structures as the polypeptide chain moves across a free-energy landscape towards its native folded state[19]. This landscape of protein folding can be classified into three structural states (Supplementary Box 1): not folded or non-native (nascent or incompletely folded protein molecules), unfolded (proteins that have lost their native 3D structure) and misfolded (proteins that are trapped in non-native conformations distinct from both the native state and the unfolded ensemble)[20,21]. The key point is that each state has different kinetic accessibilities and pathophysiological consequences. The role of the cellular proteostasis network is to prevent the accumulation of protein species in the latter two structural categories. The ability of cells to maintain proteostasis declines progressively with age, increasing the likelihood that proteins will misfold, self-associate into soluble misfolded assemblies (oligomerization) and form highly ordered, insoluble amyloid fibrils (fibrillization)[22,23].

At the molecular level, most proteins occupy metastable native folds, with kinetic barriers preventing collapse into their lowest free-energy amyloid state[22,24]. However, the proteostatic capacity declines with cellular ageing, marked by reduced chaperone efficacy, autophagy dysfunction and oxidative injury[4,24,25]. Even persistent minor destabilizations, such as oxidation or glycation, can drive partially unfolded protein intermediates that are prone to self-assembly[4,22,24,25]. For certain proteins, including apolipoproteins, IgLC and transthyretin, the amyloid state becomes thermodynamically favoured in regions

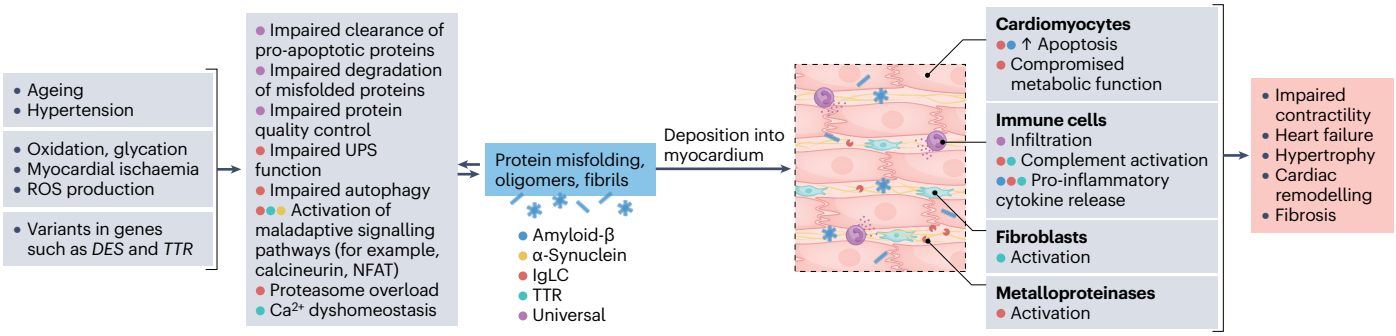


Fig. 2 | Cardiac dysfunction induced by misfolded proteins. The efficiency of cells to maintain proteostasis declines with increasing age, in conditions such as hypertension and myocardial ischaemia, with metabolic destabilization caused by oxidation, glycation or production of reactive oxygen species (ROS), or with specific gene variants. This failure of proteostasis, combined with proteasome overload and activation of maladaptive signalling pathways, increases the likelihood of protein misfolding. These misfolded proteins self-associate into oligomeric assemblies that can then progress to highly ordered, insoluble amyloid fibrils. Amyloid deposition in the myocardium leads to compromised cardiomyocyte function and increased apoptosis, activation of metalloproteinases, as well as leukocyte recruitment to the myocardium and leukocyte activation, which increase the immune response in the myocardium. These pathophysiological mechanisms lead to impaired cardiac contractility, heart failure, and cardiac hypertrophy, remodelling and fibrosis. Some of these mechanisms have been described across various proteinopathies and are considered universal, whereas others have been shown to be induced in myocardial tissue in humans by specific misfolded proteins or their oligomers and fibrils, including transthyretin (TTR), immunoglobulin light chain (IgLC), amyloid-β or α-synuclein. NFAT, nuclear factor of activated T cells; UPS, ubiquitin–proteasome system.

of increased local concentration of the protein such as in stiffened, aged vessels or stressed cardiomyocytes. Once fibrils form, fragmentation and secondary nucleation can accelerate the proliferation of pre-fibrillar species[22,24]. The main components of the cellular proteostasis network, along with disruptive events in proteostatic pathways that cause PMDs, are shown in Figs. 3 and 4. In the heart and vasculature, this global erosion of proteostasis manifests as progressive amyloid deposition, sarcomere dysfunction and endothelial injury, setting the stage for the clinical phenotypes described in the following sections.

Shared mechanisms of cardiac and vascular injury

Initiation of amyloidogenesis. In the ageing cardiovascular system, progressive failure of the proteostasis network[4,25] leads to an increase in both circulating and locally produced amyloidogenic proteins that perturb contractile, metabolic and vascular functions[23,26,27]. Proteostasis failure can also be triggered by chronic cellular stressors or other precipitators of proteinopathies, which ultimately facilitate the development of PMDs (Supplementary Figs. 1 and 2). Chaperone capacity becomes overwhelmed or transcriptionally downregulated, permitting toxic protein intermediates to escape refolding surveillance[4]. In AL amyloidosis, proteasome saturation leads to cytoplasmic accumulation of amyloidogenic IgLCs, which in turn impair cardiomyocyte contractility[28]. Similarly, amyloid-β and α-synuclein aggregates impair proteasome function, exacerbating misfolded protein burden and promoting a self-reinforcing cycle of proteotoxic stress[29].

Autophagy, another crucial degradation mechanism, is commonly disrupted in PMDs. Impaired autophagic flux, due to defective autophagosome–lysosome fusion or reduced expression of autophagy-related genes, limits the clearance of misfolded proteins and damaged organelles[30]. In the endoplasmic reticulum, accumulation of misfolded secretory proteins, such as variant transthyretin or amyloidogenic IgLC, activates the unfolded protein response (UPR), leading to maladaptive signalling through pathways such as eukaryotic translation initiation factor 2α kinase 3 (EIF2AK3; also known as PERK)–eukaryotic translation initiation factor 2α (eIF2α)–DNA damage-inducible transcript 3 protein (DDIT3; also known as CHOP). This mechanism has been implicated in Alzheimer disease and cardiomyopathies associated with both AL amyloidosis and ATTR[31–33].

Therefore, misfolded proteins impair both the ubiquitin–proteasome system (UPS) and autophagy, preventing the clearance of the misfolded proteins and leading to accumulation of toxic intermediates, further dysregulation of proteostasis and the initiation of amyloid formation in a self-reinforcing cycle of proteotoxic stress in the cardiovascular system. An alternative view of these proteostatic mechanisms and their failure is that amyloid formation is a 'last resort' mechanism that sequesters highly toxic oligomers into less toxic protein aggregates. This process could represent an evolutionarily conserved, biophysical survival pathway of partial detoxification that occurs with ageing or in younger individuals when toxic, misfolded proteins are produced due to genetic variants or cellular stress[34].

Oligomer proteotoxicity and oxidative stress. Although mature fibrils are the main finding that pathologically characterizes amyloidosis, soluble oligomeric protein species can trigger many processes that lead to cell death[35–38]. Oligomers are soluble, non-fibrillar assemblies of misfolded protein molecules, typically ranging from dimers to species containing tens of monomers. Oligomers are structurally heterogeneous, often transient, and their precise composition and conformation are difficult to characterize with current methods[39–41].

Although oligomeric species have been implicated as mediators of cellular toxicity across multiple proteinopathies, their identification and isolation are technically challenging, and the extent to which specific oligomeric conformations drive pathology is actively debated. In ATTR, protein oligomers impair cardiomyocyte calcium handling and contractility[33]. In AL amyloidosis, amyloidogenic IgLCs internalized by cardiomyocytes activate p38 mitogen-activated protein kinases, causing mitochondrial dysfunction, apoptosis and oxidative stress[28,42]. Importantly, amyloidogenic immunoglobulin free light chains (FLCs) in patients with AL amyloidosis might also be toxic directly, independent of fibril deposition[28]. Amyloid-β and α-synuclein assemblies amplify

the production of reactive oxygen species, exert adverse effects on neuronal membranes and promote synaptic dysfunction[43]. Reactive oxygen species, in turn, damage DNA, proteins and lipids, impair nitric oxide bioavailability, and further destabilize the proteostasis machinery.

The convergence of oligomer toxicity and oxidative stress provides a unifying mechanism for both cardiac and vascular damage. Cardiomyocytes undergo apoptosis, resulting in cardiac fibrosis, and endothelial cells lose vasodilatory capacity, adopt a pro-inflammatory phenotype and become prone to thrombosis[43,44]. Clinically, this convergence of oligomer toxicity and oxidative stress translates into arrhythmias, heart failure (often with preserved ejection fraction) and a vasculopathy characterized by impaired vasodilatation, microvascular ischaemia and thrombosis[45,46].

Amyloid infiltration and microvascular dysfunction. Deposition of insoluble fibrils causes predominantly mechanical, rather than cytotoxic, injury. In the myocardium, amyloid infiltrates the interstitium, thereby stiffening the ventricular wall, impairing diastolic filling and disrupting conduction tissue[47,48]. In small coronary arteries and arterioles, amyloid infiltration narrows the lumen and reduces flow reserve[47], explaining the presence of angina and ischaemia in the absence of epicardial coronary artery disease. Cerebral amyloid angiopathy (CAA)-associated microbleeds and blood–brain barrier leakage underlie cognitive decline and haemorrhagic complications. CAA is an age-related pathology but is far more prevalent and severe in Alzheimer disease than in the general population of older adults[49,50]. Interestingly, sporadic CAA does not coexist with amyloidosis in other organs. Amyloid-β deposition in sporadic CAA is largely confined to the

Table 1 | Vascular dysfunction induced by misfolded proteins

Disease	Platelets	Endothelial cells	Smooth muscle cells	Immune cells	Vascular effects
TTR amyloidosis	↑ Activation and aggregation on amyloid fibrils[289] ↑ Thrombin generation and coagulation[289] ↑ Thromboembolism risk (atrial dysfunction, atrial fibrillation)[72]	Perivascular and intravascular TTR deposition[13,87] ↑ Permeability[91] Barrier dysfunction (especially in ATTRv)[91] Dysfunction modest in ATTRwt (FMD often preserved)[191]	Early amyloid fibrils along basement membrane[290] ↑ ECM remodelling[291] ↑ Vascular stiffness Large-artery stiffness not consistently increased in ATTRwt[191]	Activation of perivascular macrophages and microglia[85,292] Phagocytosis around protein deposits[85,86] Low-grade IL-1β and TNF secretion[86]	Microvascular: intramyocardial and endoneural involvement, ↑ resistance, rarefaction[87,89] Macrovascular: large-artery elastic properties often preserved in ATTRwt, IMT variable, ↓ BP[191]
Immunoglobulin light chain amyloidosis	Activation, adhesion, degranulation[293] ↑ ROS production[293,294] Thrombosis[295] Thrombocytopenia[296] Bleeding diathesis[74]	↓ NO bioavailability[14] ↑ Oxidative stress, peroxynitrite levels[14] Dysfunction[14] ↑ Apoptosis[14] and permeability[297] Mitochondrial dysfunction[14]	Loss of contractile function[298] Macrophage-like phenotype transformation[298]	Suppression of normal haematopoiesis[299] Expansion of monocyte and $CD4^+$ T cell subsets[299] ↑ Chemokine and cytokine secretion by monocytes and macrophages[53]	Microvascular deposits, obstruction, dysfunction and ischaemia[47] Bleeding[74] Impaired vascular reactivity[197] Paradoxical vasodilatation ↑ FMD ↓ BP[197,198]
Amyloid-β-related diseases	Activation, adhesion, degranulation[66,67] ↑ ROS production[68] Thrombosis[68,69]	↓ NO bioavailability[300] ↑ Oxidative stress, peroxynitrite levels[300] ↑ Apoptosis[131] ↑ Inflammatory gene expression[301] and cytokine production[301]	Altered contractility and relaxation[302]	Monocyte activation[303] ↑ Leukocyte adhesion and migration[304] ↑ Cytokine release[303] ↑ ROS production in macrophages[305] Foam cell formation[60]	Cerebral circulation: endothelial dysfunction, vascular inflammation, microvascular ischaemia, bleeding[49,128] Extracerebral: endothelial dysfunction, vascular inflammation, accelerated atherogenesis, arterial stiffening, ↑ BP, ↑ acute coronary syndromes[123,131,202,203,206,306]
α-Synuclein aggregation	Activation, adhesion[146]	Degeneration[148] ↑ Release of vasoactive and inflammatory mediators[148]	NR	Monocyte activation[148,149] T cell activation[149] Immune cell infiltration through blood–brain barrier[148]	Infiltration and deposits lead to blood–brain barrier leakage and vessel degeneration[10] Orthostatic hypotension[146] Impaired vasoconstriction[146]
Medin amyloidosis	NR	Impaired function via AGER ↑ Oxidative stress ↑ NF-κB-dependent inflammatory response[138]	Impaired contractile function[139] ↑ Apoptosis and oxidative stress[139] Senescence drives accelerated fibril deposition (via ↑ extracellular vesicle secretion)[141]	↑ Astrocyte-mediated neuroinflammation[137] Amplification of local inflammatory responses[137]	Microvascular: deposits in cerebral microvasculature linked to vascular dementia[142] Macrovascular: accumulation in media of large arteries, direct driver of arterial ageing, ↑ PWV, cerebrovascular stiffening, loss of elastic fibre architecture, accelerated aneurysm formation[8,136,307,308]

AGER, advanced glycation end product-specific receptor; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BP, blood pressure; ECM, extracellular matrix; FMD, flow-mediated dilatation; IMT, intima–media thickness; NF-κB, nuclear factor-κB; NR, not reported; NO, nitric oxide; PWV, pulse wave velocity; ROS, reactive oxygen species; TNF, tumour necrosis factor; TTR, transthyretin.

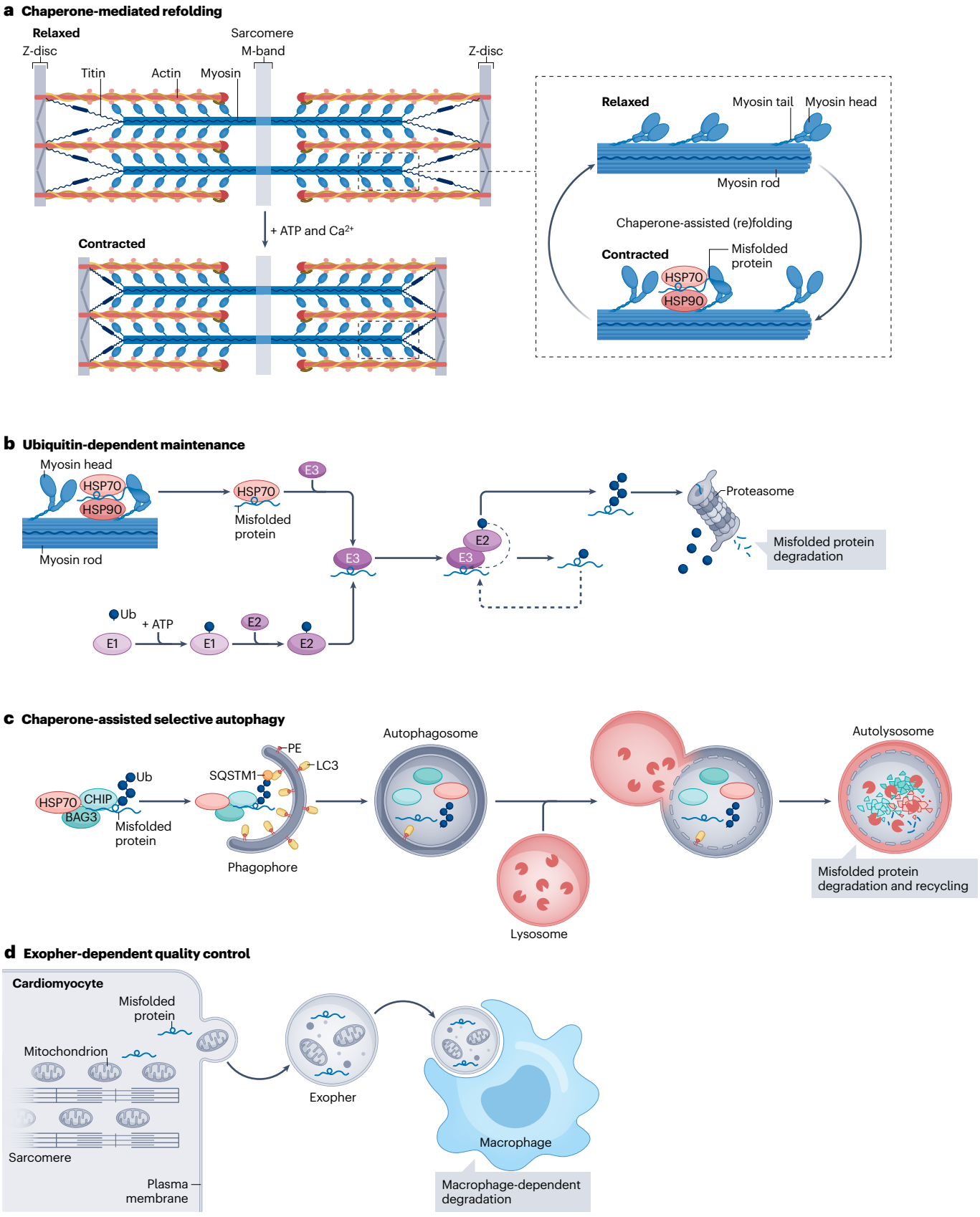

a Chaperone-mediated refolding
Relaxed
Z-disc
Titin
Actin
Myosin
Sarcomere
M-band
Z-disc
+ ATP and Ca2+
Contracted
Relaxed
Myosin tail
Myosin head
Myosin rod
Chaperone-assisted (re)folding
Contracted
Misfolded protein
HSP70
HSP90
b Ubiquitin-dependent maintenance
Myosin head
HSP70
HSP90
Myosin rod
HSP70
Misfolded protein
E3
E3
E2
E3
Proteasome
Misfolded protein degradation
Ub
+ ATP
E1
E1
E2
E2
c Chaperone-assisted selective autophagy
HSP70
CHIP
BAG3
Ub
Misfolded protein
SQSTM1
PE
LC3
Phagophore
Autophagosome
Lysosome
Autolysosome
Misfolded protein degradation and recycling
d Exopher-dependent quality control
Cardiomyocyte
Misfolded protein
Mitochondrion
Sarcomere
Plasma membrane
Exopher
Macrophage
Macrophage-dependent degradation

Fig. 3 | Proteostasis pathways safeguarding cardiomyocyte integrity. Striated muscle cells, including cardiomyocytes, rely on multiple, complementary quality control systems to preserve the structure and function of the contractile apparatus. Together, these surveillance pathways coordinate protein repair, recycling and removal to maintain contractile performance and protect the heart from proteotoxic stress. **a**, Chaperone-mediated refolding (for example, by heat shock protein 70 (HSP70) and HSP90) stabilizes and restores contractile and structural proteins that become misfolded under (mechanical) stress. **b**, Ubiquitin-dependent maintenance selectively removes proteins that cannot be refolded, preventing their toxic accumulation. Protein substrates are tagged with ubiquitin (Ub) through a three-step enzymatic cascade and subsequently degraded by the 26S proteasome. **c**, Chaperone-assisted selective autophagy enables the degradation and recycling of larger protein assemblies and aggregates through delivery to lysosomes. HSPs and their co-chaperones (the chaperome) recognize damaged clients, and ubiquitylation of the misfolded protein client facilitates chaperone–client recruitment to the autophagosome for lysosomal degradation. **d**, Exopher-mediated quality control allows the expulsion of damaged material, including mitochondria and misfolded proteins, into extracellular-vesicle-like structures termed exophers, which are then removed by macrophages. BAG3, BAG family molecular chaperone regulator 3; CHIP, E3 ubiquitin-protein ligase CHIP; E1, ubiquitin-activating enzymes; E2, ubiquitin-conjugating enzymes; E3, E3 ubiquitin ligases; LC3, microtubule-associated proteins 1A/1B light chain 3; PE, phosphatidylethanolamine; SQSTM1, sequestosome 1.

central nervous system, where local amyloid precursor protein processing and tissue-specific clearance pathways favour its accumulation in cerebral vessels. By contrast, systemic amyloid types, such as serum amyloid A (SAA), IgLC-derived amyloid and transthyretin amyloid, arise from biochemically distinct precursor proteins and show different patterns of tissue deposition[51].

Microvascular dysfunction in PMDs is often attributed to proteotoxic injury. However, many patients with PMD and microvascular dysfunction are older and have substantially increased cardiometabolic risk compared with the general population, which can independently drive microvascular remodelling. Therefore, distinguishing between microangiopathy directly driven by protein aggregation and microvascular disease related to diabetes mellitus or hypertension is challenging, particularly in cross-sectional studies. Prospective studies combining standardized microvascular function testing with quantitative measures of proteotoxic burden across disease stages will be required to provide definitive evidence.

Amyloid-induced inflammation and fibrosis. Misfolded proteins and their pre-fibrillar species can elicit inflammatory responses. In the heart, amyloidogenic IgLCs stimulate matrix metalloproteinases and drive extracellular matrix degradation[42], whereas transthyretin oligomers activate fibroblasts to deposit collagen, amplifying interstitial fibrosis[52]. IgLC amyloid deposition in human cardiac cells triggers activation of the NLRP3 inflammasome and upregulates the expression of complement factors, cytokines (such as IL-1β) and chemokines, increasing local immune responses[53]. Similarly, activation of the complement system and immunoglobulin proteins has been reported in myocardial proteomic profiling studies of patients with cardiac ATTR[54]. Biopsy samples from patients with cardiac AL amyloidosis or ATTR showed myocardial infiltration by macrophages, neutrophils and T cells[55]. Moreover, patients with AL amyloidosis and intramyocardial inflammation (predominantly mediated by lymphocyte infiltration) had higher mortality than those without intramyocardial inflammation or patients with ATTR with or without intramyocardial inflammation[55]. In addition to their role in amyloid formation and disease progression, macrophages contribute to amyloid absorption[56,57]. Although this concept is not new, more data are needed on the mechanisms of macrophage-mediated amyloid absorption and the biochemistry of macrophage-driven amyloid destruction or disassembly[58]. In the vasculature, amyloid-β induces foam cell formation as well as microglia and astrocyte activation, which release pro-inflammatory cytokines, such as IL-1β and tumour necrosis factor (TNF), that perpetuate vascular inflammation and damage[59–61]. Chronic inflammation coupled with fibrotic remodelling reduces compliance in both the myocardium and vessels, producing restrictive haemodynamics.

The differential organ response to PMD treatments is important in amyloidosis. For example, in both patients with cardiac AL amyloidosis and patients with ATTR, treatment can lead to substantial improvements in cardiac function and biomarker profiles, and even to normalization of cardiac biomarkers, without corresponding changes in cardiac imaging parameters[62,63]. However, in the liver, the amyloid load can regress after treatment, sometimes reflected by a reduction in liver size[64]. Whether macrophage abundance in the liver contributes to amyloid clearance or the activity of these cells becomes quiescent following a reduction in amyloidogenic protein production with treatment, is unclear.

An unresolved question is whether inflammation is a primary driver of disease progression or is predominantly a secondary response to proteotoxic injury and tissue remodelling. Human cardiac biopsy studies demonstrate immune infiltration and fibrosis, but samples are usually obtained at clinically overt disease stages and could be influenced by treatments. Therefore, anti-inflammatory therapeutic approaches might be beneficial only in specific inflammatory endotypes and within limited time windows. This concept reinforces the need for mechanistic phenotyping, rather than assuming uniform inflammatory cardiomyopathy across PMDs.

Amyloid–platelet interactions and thrombosis. Proteins with amyloidogenic properties can activate platelets, potentially contributing to the increased atherothrombotic risk observed in amyloid-associated diseases[3]. Amyloid-β, which is produced not only in the central nervous system but also by activated platelets themselves[65], binds to platelet receptors, such as platelet glycoprotein VI[66], integrin αIIbβ3 (ref. 67) and platelet glycoprotein 4 (also known as CD36), provoking platelet activation and aggregation. Patients with Alzheimer disease have elevated numbers of preactivated circulating platelets, and these platelets can contribute to cerebrovascular dysfunction and systemic atherothrombosis[68,69]. In PMDs, soluble assemblies of misfolded proteins can prime platelets and coagulation pathways, potentially explaining the paradox of heightened thromboembolic risk even in sinus rhythm and in the absence of large-vessel atherosclerosis[3,70]. Autopsy evidence indicates that patients with AL amyloidosis have a higher frequency of intracardiac thromboses and fatal embolic events compared with healthy individuals or patients with other types of cardiac amyloidosis[71]. Atrial myopathy, impaired contractile function and atrial fibrillation have been proposed as underlying mechanisms leading to the increase in thrombotic events among patients with cardiac amyloidosis, and immunomodulatory drugs might additionally increase

Box 1 | General mechanisms of protein quality control

Proteostasis network

- Proteostasis is the finely regulated production and folding of proteins, together with the clearance of short-lived, unfolded, misfolded and/or damaged proteins. Proteostasis is essential for cellular functional integrity, homeostasis and survival, particularly in postmitotic cardiomyocytes, which are prone to the accumulation of misfolded proteins due to the high metabolic demand and limited regenerative capacity of these cells[334].
- Molecular chaperones, the ubiquitin–proteasome system (UPS), the autophagy–lysosome pathway and other stress-response pathways function cooperatively to initiate de novo protein folding, detect not-folded, unfolded or misfolded polypeptides, and either refold or selectively degrade damaged proteins[334].
- Proteostasis capacity constrains disease kinetics. In a case of 'domino' liver transplantation (in which an already transplanted liver is re-transplanted into a second patient), a recipient developed iatrogenic transthyretin amyloidosis within a few years of receiving a liver transplant from a donor with familial amyloidotic polyneuropathy (Val30Met *TTR* variant)[335]. The remarkable acceleration of the disease in the domino recipient compared with the donor suggests reduced proteostasis capacity in the recipient[335]. Although differences in amyloidogenic precursor load and comorbidities might also contribute to disease acceleration, the markedly faster kinetics in the recipient suggest a ceiling effect of host proteostasis capacity on disease tempo.

Chaperones

- A diverse collection of molecular chaperones and co-chaperones, as well as chaperone regulators and adaptors[31,336].
- These molecules maintain a balance in nascent polypeptides between 'fold, hold or degrade', and support protein sorting and trafficking[31,336].
- Chaperones prevent proteome instability and aggregation[31,336].
- Chaperone-mediated autophagy or the UPS selectively degrade polypeptides that unfold or misfold because of genomic-mediated instability or exposure to excessive stressors (such as reactive oxidative species)[337,338].

Ubiquitin–proteasome system

- The UPS mediates the turnover of soluble proteins in the cell[337].
- The UPS is a highly specialized pathway that degrades both short-lived functional proteins (mainly nucleo-cytosolic regulatory proteins) and non-functional (unfolded, misfolded or non-native) polypeptides before they form insoluble aggregates[337].
- Proteolytic cleavage of the substrate protein is mediated by a multienzyme complex, namely the 26S proteasome.
- Targeted degradation of a substrate protein via the UPS requires the ATP-dependent conjugation of ubiquitin, mediated by an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, which orientates the ubiquitin for attachment, and a specialized E3 ubiquitin ligase, which confers substrate specificity[339].
- Substrate proteins can be modified by addition of a single ubiquitin molecule (monoubiquitylation) or multiple ubiquitin molecules (multi-monoubiquitylation)[339].
- To date, only a few E3 ubiquitin ligases have been associated with their specific substrates in cardiomyocytes. The E3 ubiquitin-protein ligase CHIP works with the chaperones heat shock protein 70 (HSP70) and HSP90 to redirect misfolded proteins for degradation, protecting cardiomyocytes from stresses such as doxorubicin-induced injury[340,341].
- In chaperone-assisted selective autophagy, CHIP–BAG3 (BAG family molecular chaperone regulator 3) complexes ubiquitylate proteins, such as desmin, filamin C and tropomyosin, for lysosomal clearance, thereby maintaining sarcomeric integrity and excitation–contraction coupling[342,343].
- Other E3 ubiquitin ligases also support cardiac proteostasis. Muscle-specific RING finger proteins degrade key sarcomeric proteins and protect against hypertrophy[344,345]. F-box only protein 32 regulates hypertrophic signalling via activation of Forkhead box protein O and inhibition of calcineurin, thereby limiting fibrosis and maladaptive remodelling in the ageing heart[346–348].

Autophagy–lysosome pathway

- Involves macroautophagy and microautophagy (as well as chaperone-mediated autophagy), which remove (among other cellular components) protein aggregates and damaged cellular organelles (such as mitochondria via mitophagy)[349].
- Can be activated by metabolic signals (for example, starvation or fasting) to maintain cellular homeostasis by replenishing cellular energy resources[268,338].
- Uses lysosomes as an end point sink to degrade and recycle damaged organelles, long-lived proteins, aggregated ubiquitinated polypeptides, polypeptides modified by non-enzymatic post-translational modifications (non-UPS degradable), and other unnecessary and potentially toxic cellular components[268,338].
- Crucial for bulk degradation–recycling and clearance of aggregates.

Stress-response pathways

- Mobilize cytoprotective programmes upon proteotoxic stress or proteome instability[31].
- Include the cytosolic heat-shock response (such as heat shock factor protein 1) and the endoplasmic reticulum unfolded protein response mediated by serine–threonine-protein kinase–endoribonuclease IRE1, eukaryotic translation initiation factor 2α kinase 3, and cyclic AMP-dependent transcription factor ATF6 (ref. 31), as well as the Kelch-like ECH associated protein 1–nuclear factor erythroid 2-related factor 2 antioxidant signalling pathway[350].
- Promote chaperone binding to misfolded proteins, increase protein folding and degradation capacity, modulate cell energetics, and attenuate cell oxidative load as well as global protein translation to reduce the proteotoxic load[31].

thrombotic risk in patients with systemic amyloidosis[72,73]. Additionally, patients with AL amyloidosis present coagulation abnormalities, hyperfibrinolysis caused by elevated levels of plasmin–α2-antiplasmin, and an increased frequency of bleeding complications[74,75].

The exact mechanisms by which amyloids differentially affect platelet function and coagulation pathways, increasing the risk of thrombosis and vascular complications, are not well defined. From a clinical standpoint, the thrombotic phenotype in systemic

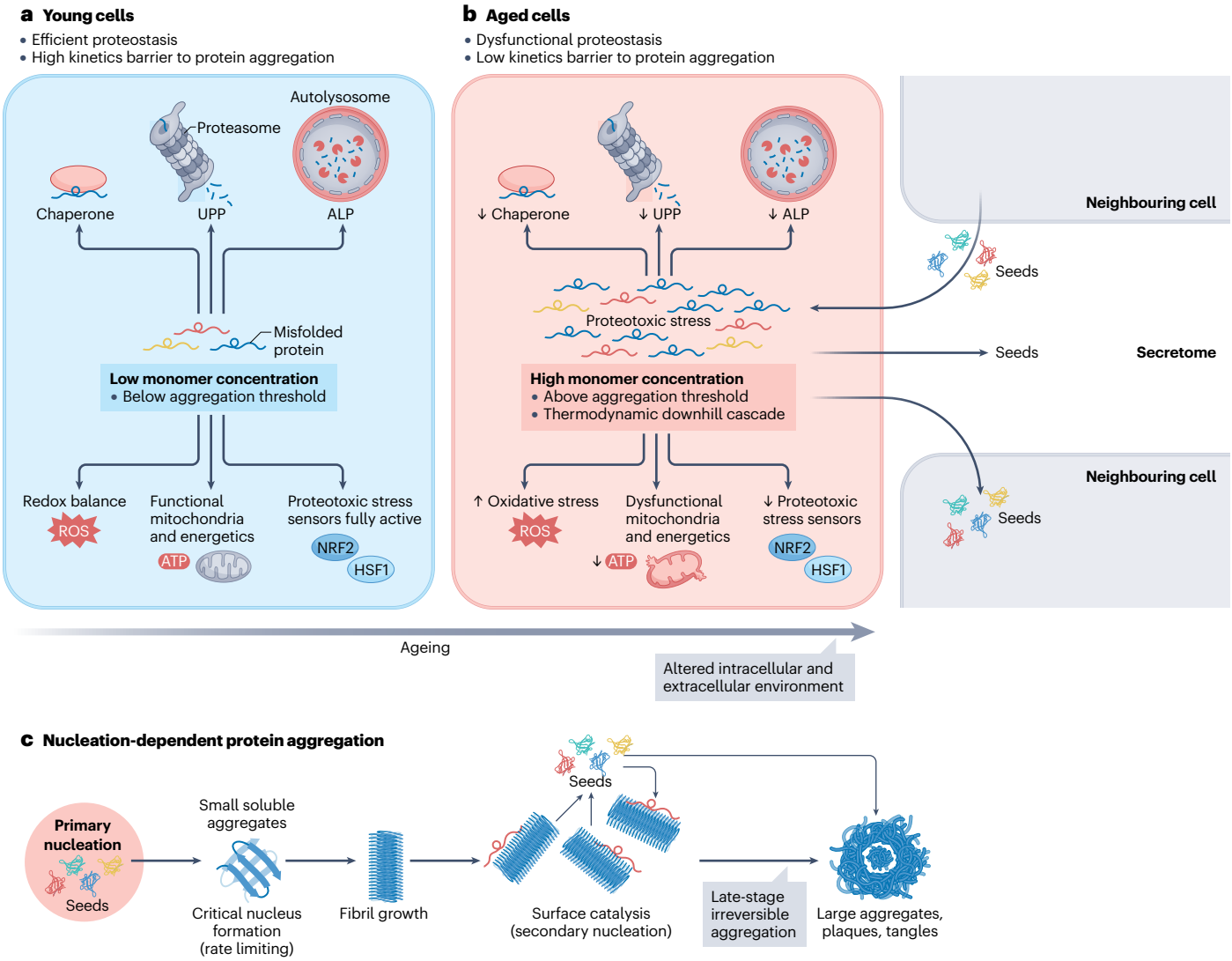


Fig. 4 | Loss of proteostasis triggers polypeptide aggregation and seeding in ageing and disease. a, In young cells, efficient proteostatic mechanisms, including the chaperome, the ubiquitin–proteasome pathway (UPP) and the autophagy–lysosome pathway (ALP), maintain levels of unfolded or misfolded protein monomers below the critical concentration required for aggregation. Functional mitochondria support, among other things, adequate energetics (ATP production), and redox balance and stress-response pathways (such as nuclear factor erythroid 2-related factor 2 (NRF2) and heat shock factor protein 1 (HSF1)) are fully active. Overall, efficient cellular proteostasis maintains aggregation-prone polypeptide species below the critical concentration threshold for aggregation, thereby limiting supersaturation, and kinetic barriers further suppress nucleation[22,24]. **b**, With ageing, proteostatic machineries collapse, leading to widespread proteotoxic stress and accumulation of unfolded or misfolded polypeptides (which can also result from genomic instability). Impairment of mitochondrial functionality, reduced ATP levels, increased levels of reactive oxygen species (ROS) and dysfunctional stress-response signalling contribute to an intracellular environment where unfolded or misfolded protein monomers can exceed the critical concentration threshold for aggregation. This milieu triggers a thermodynamic downhill cascade in which protein aggregation becomes energetically favourable. **c**, Polypeptide aggregates can serve as seeds or nucleation centres to propagate and accelerate the conversion of soluble proteins to polypeptide aggregates (fibrils) through nucleation-dependent mechanisms (right). Primary nucleation generates new aggregates from soluble precursor species, which can subsequently grow by elongation through the addition of further soluble protein molecules. Once aggregates have formed, secondary processes, including fibril fragmentation and surface-catalysed secondary nucleation, can generate additional aggregates and thereby accelerate the proliferation of aggregates, ultimately leading to the accumulation of fibrillar assemblies and larger deposits, including plaques and tangles. Small seeds are also taken up from the cell secretome by neighbouring cells, bypassing the primary nucleation barrier and accelerating the aggregation cascade across tissues.

amyloidosis is complicated by simultaneous bleeding risk, particularly in AL amyloidosis. Much of the evidence in humans is retrospective and enriched for patients with atrial myopathy or atrial fibrillation, limiting attribution to proteotoxic platelet function alone. As a result, although the involvement of platelet activation is mechanistically compelling, prospective studies are required before expanding antithrombotic strategies beyond guideline-based indications.

Tissue tropism by strains and genotype. A peculiarity of amyloidogenic proteins is their ability to acquire more than one self-templating fold, leading to the formation of various amyloid fibril polymorphs with distinctive tinctorial properties, patterns of tissue deposition and fragmentation, organ tropism, and clinical phenotypes. Although this phenomenon was initially thought to be confined to prion diseases, leading to the formulation of the concept of prion strains[76,77], it is now recognized in a wide range of PMDs.

The identification of amyloid fibril polymorphs has been facilitated by the use of cryogenic electron microscopy (cryo-EM), which improves visualization of protein 3D structures[78,79]. Cryo-EM with gold nanoparticle labelling enables the precise characterization of fibrillar polymorphs of various amyloid proteins, including α-synuclein, amyloid-β and amyloidogenic IgLC. This technique requires very small amounts of tissue and no need for advanced sample processing[79]. In ATTR, cryo-EM has revealed promising therapeutic targets by improving the structural characterization of transthyretin conformations in the presence or absence of ligands[78].

Genotype–phenotype correlations also contribute to the heterogeneity of clinical presentation in PMDs, with the disease-causing DNA sequence variant influencing amyloid organ tropism, including cardiac and vascular involvement, and clinical phenotype. In ATTR, a continuous spectrum of clinical presentations exists between the 'wild-type' gene encoding transthyretin (*TTR*) and *TTR* variants that predominantly affect the heart (cardiac phenotype), such as Val122Ile, or *TTR* variants that predominantly affect the peripheral and autonomic nervous system (neurological phenotype), such as Val30Met, which is associated with early-onset disease. Most variants lie between these two extremes of clinical presentation, being associated with a combination of both cardiac and neurological involvement (mixed phenotype)[80]. For example, the Val30Met *TTR* variant can produce either early-onset neuropathic or late-onset cardiomyopathy phenotypes depending on fibril type and additional modifiers, illustrating how strain type and genotype jointly shape the organ tropism of the strain. Further characterization of strain types and gene variants correlated with cardiovascular involvement in PMDs could improve the diagnosis and treatment of PMDs.

Organ involvement in amyloidosis is likely to reflect complex local factors, including biochemical, mechanical and immunological conditions, as well as resident cell populations, which explains why certain tissues are preferentially affected despite systemic protein production. High-resolution structural analyses of patient-derived fibrils using cryo-EM could provide evidence to support the link between clinically distinct phenotypes and individual fibril conformations, providing a mechanistic basis for heterogeneity in tissue tropism and fibril templating properties. However, datasets are typically derived from brain and heart tissue samples from patients with end-stage disease and selected clinical contexts, and do not provide prognostic information or guide clinical decisions. Therefore, we currently view cryo-EM as immediately actionable for mechanistic subclassification and rational therapeutic targeting, with prospective validation needed to link specific structures to clinical trajectories and treatment response.

Disease-specific pathways

Transthyretin amyloidosis. ATTR can be caused by *TTR* variants (hereditary ATTR) or associated with age-related conditions (wild-type ATTR)[6], which could represent a distinct phenotype of accelerated vascular ageing. Native transthyretin is primarily synthesized in the liver and the choroid plexus and circulates as a homotetramer composed of four identical monomers in a β-sandwich fold[11]. However, the natural cycle and feedback loops of transthyretin are not fully understood; specifically, why stabilizing the transthyretin tetramer (for example, with acoramidis or tafamidis) increases its level in serum, and whether this protein conformation is ultimately beneficial or not. Several factors, including post-translational modifications, age-related oxidative stress, shear stress and the presence of metal cations, can destabilize the transthyretin tetramer leading to its dissociation into dimers and monomers[23,81–83]. These monomeric transthyretin species are rich in β-strands and prone to misfolding. The monomers form dimers first and then associate into spherical hexamers, which are early soluble assemblies and serve as a building block to self-assemble into oligomers[84]. Cytotoxic monomers, together with spherical hexamers, provide the scaffold for amyloid fibril formation[81].

Myocardial inflammation, characterized by macrophage and T cell infiltration following the secretion of pro-inflammatory mediators by cardiac fibroblasts induced by transthyretin aggregates (Fig. 2), is present in about one-third of patients with ATTR cardiomyopathy and is associated with an increased risk of hospitalization for heart failure and death compared with patients with ATTR without inflammation[85,86]. Although myocardial infiltration is the dominant feature of ATTR, the presence of vascular involvement is increasingly recognized[87]. Transthyretin amyloid fibrils can infiltrate and deposit in small, medium and large arteries[12,13]. Amyloid fibrils originating from misfolded transthyretin accumulate inside the vasculature, often with perivascular and parenchymal tissue deposits[13,87]. In hereditary ATTR, certain *TTR* variants (such as Val30Met) are associated with substantial vascular involvement, especially in the leptomeningeal and peripheral nerve vasculature, leading to cerebrovascular and neuropathic consequences[88–90]. Emerging evidence suggests that transthyretin deposition can directly induce vascular endothelial injury in patients with ATTR. In a study published in 2026, both recombinant transthyretin and serum from patients with ATTR induced oxidative and proteotoxic stress in human umbilical vein endothelial cells in vitro, reducing endothelial viability and migration and increasing the formation of aggresomes[91]. Crucially, tafamidis attenuated these effects in vitro and improved arterial stiffness in patients with ATTR[91], supporting a potential vasculoprotective effect of this drug.

In ATTR, fibril types are heterogeneous. Type A fibrils, which contain both full-length and fragmented transthyretin, are typically weakly congophilic (faint staining with Congo red, a dye used to identify amyloid deposits) and show avid binding to bone-seeking radiotracers[92–94]. By contrast, type B fibrils are composed predominantly of full-length transthyretin, are more strongly congophilic and often show lower bone-tracer binding[92–94]. Clinically, type A fibrils are often associated with predominant cardiac involvement and positive findings on bone scintigraphy, whereas type B fibrils are closely linked to early-onset neuropathic phenotypes and can yield false-negative findings on bone scintigraphy[92–94]. However, direct evidence that fibril strain alone determines spatial transthyretin deposition in the myocardium or

vasculature, or preferentially targets the nervous system, is lacking. Findings derive largely from cross-sectional or disease-stage-selected cohorts, and fibril composition can evolve during disease progression. Thus, differences in strain types are a possible explanation for the phenotypic diversity in ATTR but should not yet be presented as a fully validated determinant of cardiovascular tropism.

AL amyloidosis. In AL amyloidosis, IgLCs produced by clonal plasma cells circulate as unbound FLCs, which misfold and aggregate into soluble oligomers and insoluble fibrils. Insoluble fibrils deposit in tissues and drive organ dysfunction[7]. Beyond intrinsic sequence determinants, microenvironmental cofactors, including glycosaminoglycans and extracellular chaperones, modulate IgLC nucleation and fibril elongation. A critical threshold of circulating levels of amyloidogenic IgLCs seems to be necessary to initiate fibrillogenesis[7]. IgLC-derived amyloid infiltration and direct toxicity in the myocardium first cause impaired cardiac relaxation, which progresses to typical restrictive physiology as the disease advances[95]. The effects of amyloidogenic FLCs on cardiac fibroblasts and cardiomyocytes include increased oxidative stress and apoptosis, as well as decreased cardiac contractility and relaxation[96].

Autopsy studies of individuals with AL amyloidosis show that IgLC-derived amyloid fibrils are deposited predominantly in the media of small-sized and medium-sized arteries and veins in multiple organs and tissues[97–102]. Once deposited in blood vessels, the amyloids can induce vascular injury and impaired vasoreactivity[14]. Extensive coronary vascular deposits of IgLC-derived amyloid lead to increased microvascular resistance and limited vasodilatory capacity[87,103]. Extravascular intramyocardial IgLC-derived amyloid deposits can also induce microvascular ischaemia through obstruction of the vasa vasorum[104]. At the microvascular level, evidence from case-series and retrospective studies suggests that endothelial dysfunction, arterial wall fragility and obstruction from vascular amyloid deposition are the mechanisms underlying and preceding many manifestations of AL amyloidosis, such as myocardial ischaemia in the absence of epicardial coronary artery stenosis, neuropathy, myopathy, renal dysfunction, malabsorption, abnormal gastrointestinal mobility, gastrointestinal or intracranial bleeding, and jaw claudication[97–102]. Microvascular injury is also mediated by amyloidogenic FLC-induced endothelial dysfunction and apoptotic injury in endothelial cells due to oxidative stress, reduced nitric oxide bioavailability and peroxynitrite production[14]. Macrovascular involvement is intertwined with autonomic dysfunction caused by small fibre neuropathy, vascular sympathetic denervation and impaired autonomic control of vascular reactivity, resulting in orthostatic hypotension and low blood pressure in patients with AL amyloidosis[105].

Organ tropism reflects both amyloidogenic precursor load and light-chain sequence[106]. Approximately 80% of amyloidogenic IgLCs belong to the λ isotype, and certain IgLC germline gene families are associated with a strong bias towards cardiac involvement[107,108]. Specifically, the germline gene *IGLV1-44* (which encodes immunoglobulin-λ variable 1–44) is consistently associated with predominantly cardiac involvement, even if the presence of variants in other genes makes each amyloidogenic IgLC unique for each patient, introducing a layer of patient-specific complexity[109,110]. Importantly, toxicity is not limited to deposited fibrils. A direct proteotoxic effect of amyloidogenic IgLCs in cardiac tissue has been consistently demonstrated in preclinical studies, complementing the more slowly evolving damage from fibrillar deposition[42,111].

Amyloid-β-related disorders. Amyloid-β peptides, mainly amyloid-β_{40} ($A\beta_{40}$) and $A\beta_{42}$, derive from proteolytic cleavage of amyloid-β precursor protein mediated first by β-secretase and then by γ-secretase. $A\beta_{40}$ is the predominant species in CAA[112], whereas $A\beta_{42}$ and the $A\beta_{40}$-to-$A\beta_{42}$ ratio are central to Alzheimer disease pathology[113,114]. Although amyloid-β has traditionally been studied in the context of neurodegeneration, $A\beta_{40}$ is produced by vascular cells and cardiomyocytes and is detectable in the blood circulation[8,115]. Cardiometabolic risk factors, such as hypertension, diabetes, dyslipidaemia, smoking and a high-fat diet, are associated with increased circulating levels of $A\beta_{40}$, raising the possibility that amyloid-β has a role in vasculopathies of the heart–brain–vascular axis such as CVD and dementia[8,115]. Alzheimer disease and coronary artery disease share multiple pathogenetic mechanisms and risk factors[116–119], and amyloid-β metabolism has emerged as a shared pathophysiological link in most of these shared factors[120–123]. Experimental data indicate that amyloid-β, particularly $A\beta_{40}$, can directly injure the endothelium and myocardium and can alter calcium handling and impair contractility in cardiomyocytes[124,125] (Fig. 2). Furthermore, $A\beta_{40}$ exerts cytotoxic effects in cardiomyocytes, with the highest concentrations of $A\beta_{40}$ in patients with Alzheimer disease and cardiomyopathy[124,125]. These observations align with epidemiological associations between high circulating levels of $A\beta_{40}$ and an increased risk of incident heart failure[126].

Predominantly $A\beta_{40}$, but also $A\beta_{42}$, show affinity for the arterial wall, and experimental studies support pro-atherogenic and pro-inflammatory effects[3,127,128]. Amyloid-β-mediated vascular injury can occur in both cerebral and extracerebral tissues and is likely to be shaped by tissue-specific peptide handling, impaired clearance of amyloid-β, and the balance between central and peripheral amyloid-β pools[114,124,129,130]. In aortas with atherosclerotic lesions from older individuals, $A\beta_{40}$ is the predominant amyloid-β peptide, and experimental models suggest that elevated levels of $A\beta_{40}$ can promote foam cell formation, platelet activation, oxidative stress and vascular inflammation[3,60,114,131]. In addition, epidemiological studies have revealed associations between Alzheimer disease and increased arterial stiffness and other adverse vascular phenotypes[132]. Although these observations suggest that amyloid-β might be an amplifier of systemic atherosclerosis or vascular ageing in humans, shared upstream drivers, such as age, metabolic dysfunction, endothelial injury and impaired clearance pathways, could also contribute to both increased amyloid-β burden and worse vascular health. Therefore, amyloid-β might amplify vascular injury in susceptible individuals but its role as a primary causal factor merits further investigation (Boxes 2 and 3).

Taken together, the literature on amyloid-β supports mechanistic relevance to cardiovascular dysfunction, but not uniform causal certainty. Experimental data indicate that $A\beta_{40}$ has direct endothelial, inflammatory and myocardial effects, whereas human data remain largely associative (such as biomarker co-segregation with vascular disease)[114]. Epidemiological studies suggest that circulating $A\beta_{40}$ also serves as a marker integrating vascular ageing, atherosclerotic burden and impaired amyloid-β clearance. By contrast, genotype–phenotype data linking variations in the amyloid-β pathway to specific cardiac or systemic vascular presentations are sparse, even though distinct amyloid-β strains are known to influence aggregation kinetics, deposition patterns, glial responses, and recruitment of $A\beta_{40}$ and $A\beta_{42}$ peptides[133]. The key unresolved issue is whether amyloid-β primarily initiates cardiovascular injury, accelerates pre-existing CVD or simply accumulates in parallel to cardiovascular injury. Currently, no therapeutic interventions to modulate the metabolism of $A\beta_{40}$ are available.

Box 2 | Knowledge gaps and challenges in the diagnosis and management of cardiovascular involvement in protein misfolding diseases

Diagnosis

Transthyretin amyloidosis

- Unknown incidence and prevalence.
- Under-diagnosis and low awareness of clinical suspicion.
- Validation of and access to digital artificial intelligence-based screening tools remain low.
- Uncertain accuracy of bone tracers to detect transthyretin aggregates on bone scintigraphy in patients with early-stage disease and minimal myocardial amyloidosis.
- Unknown specificity and sensitivity of various bone tracers to detect transthyretin aggregates on bone scintigraphy.
- Difficulties in detecting microvascular and macrovascular impairment.
- The diagnostic value of markers of vascular involvement is unknown.
- Why do some vascular tests produce false negative results?

Immunoglobulin light chain amyloidosis

- Delayed diagnosis leads to high mortality.
- Validation of and access to digital artificial intelligence-based screening tools remain low.
- Difficulties in detecting microvascular and macrovascular impairment.
- The diagnostic value of markers of vascular involvement is unknown.

Amyloid-β associated diseases

- Whether extracerebral deviation towards the β-amyloidogenic pathway constitutes the backbone of a distinct protein misfolding disease of the cardiovascular system is unknown.
- Lack of a standardized, clinically applicable method to reproducibly measure circulating amyloid-β_{40} and amyloid-β_{42}.
- Lack of an optimal diagnostic method to identify cardiovascular involvement.
- Difficulties in detecting microvascular and macrovascular impairment.

Parkinson disease

- What is the clinical relevance of cardiac and vascular involvement?
- Lack of an optimal diagnostic method to identify cardiovascular involvement.
- Difficulties in detecting microvascular and macrovascular impairment.

Management

Transthyretin amyloidosis

- Whether transthyretin-targeted treatments lead to vascular improvement, and the effects on outcomes, is unknown.
- Current therapies (transthyretin stabilizers and *TTR* mRNA silencers) slow disease progression but do not reverse disease, and residual cardiovascular risk remains.
- The choice between transthyretin stabilizers, *TTR* mRNA silencers or combination therapy is uncertain.
- No treatments are available for advanced heart failure (NYHA class IV).
- Which patients should receive which heart failure therapies is unclear.

Immunoglobulin light chain amyloidosis

- Risk stratification needs to be improved.
- Residual cardiovascular risk remains after treatment with anti-plasma cell therapies.
- After haematological remission, the clinical relevance of increases in levels of cardiac biomarkers is uncertain.

Amyloid-β associated diseases

- What is the clinical utility of circulating levels of amyloid-β_{40} as a prognostic biomarker?
- Whether targeting amyloid-β_{40} by leveraging the off-target effects of some cardiovascular medications or by repurposing amyloid-β-specific treatments used for Alzheimer disease improves outcomes in cardiovascular disease is unknown.

Parkinson disease

- What is the clinical value of treatments specifically targeting orthostatic hypotension?
- Do amyloid-targeting treatments improve vascular involvement?

Until such agents can be investigated, genetic studies, including Mendelian randomization analyses, should further explore causal associations between amyloid-β and CVD. At present, the most balanced conclusion is that amyloid-β is an emerging prognostic cardiovascular biomarker that is mechanistically plausible and potentially pathogenic in some cardiovascular contexts. However, the extent, timing and clinical generalizability of these effects, and the role of amyloid-β as a potential therapeutic target, remain insufficiently defined.

Medin as a mediator of amyloid co-pathology. Medin, a peptide derived from lactadherin, is the most prevalent human amyloid described so far. Medin silently accumulates in the media layer of the aorta and large cerebral, coronary and peripheral arteries in nearly all individuals aged >50 years[9,15,134]. Genetic, experimental and histopathological evidence positions medin not merely as a passive bystander but as a candidate mediator of arterial ageing[9], vascular stiffening and aneurysm formation[135,136]. Furthermore, in the brain, an elevated level of medin has been linked to astrocyte-mediated neuroinflammation and correlates with vascular dementia[137]. At the cellular level, medin oligomers disrupt endothelial and smooth muscle cell function, triggering oxidative stress and localized inflammatory cascades that drive vascular degradation[138–141] (Table 1).

Beyond its intrinsic vascular toxicity, medin acts as a scaffold that facilitates the deposition of other amyloid proteins. Arterial medin aggregates are increased in patients with Alzheimer disease who have cerebral amyloid-β angiopathy[142]. Medin colocalizes with vascular

amyloid-β, forming heterologous amyloid-β–medin fibrils[143]. Moreover, medin cross-seeds the aggregation of amyloid-β both in vitro and in vivo. Accordingly, in vitro antibody-mediated immunodepletion of medin prevents this cross-seeding, and genetic deletion of medin attenuates cerebral amyloid-β angiopathy and micro-haemorrhage load in the APP23 mouse model of Alzheimer disease[143]. Similarly, medin colocalizes with SAA[144] and transthyretin amyloid in human aortic wall and aortic valves, whereas transthyretin reduces medin toxicity when co-aggregated[16]. Medin exemplifies a principle of growing importance in the field — that the various amyloidogenic proteins do not aggregate in isolation. The cross-β conformation that underlies amyloid fibril formation is a generic structural state that can be achieved by any polypeptide chain. The consequence is that amyloidogenic species with sequence or structural homology can co-aggregate and cross-seed one another[143]. This observation reflects the thermodynamic and kinetic logic of nucleation-dependent polymerization, whereby pre-formed aggregates of one protein can lower the free-energy barrier for the nucleation of another. Whether the successful targeting of one proteinopathy would improve the outcomes of another proteinopathy owing to cross-seeding mechanisms merits further investigation. Emerging evidence positions medin as a candidate mediator of arterial ageing and vascular co-pathology, making this amyloidogenic species a priority target for future mechanistic and clinical investigation (Box 3).

α-Synucleinopathies. α-Synucleinopathies extend the proteostasis paradigm to neurogenic cardiovascular dysfunction, in which

Box 3 | Strategies to address knowledge gaps in protein misfolding diseases

Molecular pathways

Pathophysiology

- Characterize microenvironments favouring amyloidogenesis.
- Decipher spatiotemporal coordination of protein quality control.
- Identify inter-tissue signalling mechanisms regulating protein quality control.
- Explore synergistic cross-β-amyloid structures and the clinical implications of co-aggregation (such as co-existence of transthyretin amyloidosis (ATTR) and immunoglobulin light chain amyloidosis (AL amyloidosis), or concurrent Alzheimer disease and Parkinson disease).

Molecular pathways as novel therapeutic targets

- Explore cell-type-specific modulation of protein quality control.
- Investigate exopher formation and macrophage-mediated clearance of amyloids.
- Define the roles of autophagy and proteasome-mediated degradation in ameliorating cardiac dysfunction.

Cross-species findings

- Translate findings from simple experimental model organisms to mammalian cardiac tissues.
- Focus on integrated systems-biology approaches.

Diagnosis

Awareness and lack of clinical suspicion

- Broaden the use of screening tools.
- Establish the clinical and prognostic value of multiparametric risk tools in ATTR and AL amyloidosis.
- Incorporate the assessment of cardiac and vascular involvement into standard diagnostic workflows for protein misfolding diseases, including ATTR, AL amyloidosis, Alzheimer disease and Parkinson disease.
- Establish centres of excellence for patient referral and management (ATTR, AL amyloidosis, Alzheimer disease, Parkinson disease).

Blood biomarkers and scoring systems for vascular involvement

- Validate biomarkers of vascular dysfunction (ATTR, AL amyloidosis, Alzheimer disease).
- Define and standardize reference values (diagnostic and prognostic) for circulating amyloid-β peptides (Alzheimer disease).
- Investigate medin as a potential biomarker or mediator of arterial ageing and vascular amyloid co-pathology.

Role of artificial intelligence

- Conduct randomized, controlled trials to assess artificial intelligence-enhanced diagnostic and prognostic pathways (ATTR, AL amyloidosis).

Management

- Clinical trial design
  - Define robust surrogate end points and stratify patients based on molecular, genetic and imaging phenotypes.
  - Establish multimodal approaches to capture treatment effects on residual cardiovascular risk.
  - Apply therapeutic strategies (such as protein stabilizers, chaperones and proteasome modulators) proven to be efficacious in other conditions, along with trial designs shown to be successful across different diseases.
- Conduct individual participant data meta-analyses with high sample sizes.
- Narrow the gap between clinical efficacy and real-world effectiveness (access, tolerability and long-term monitoring).
- Develop investigational therapies that promote removal of existing amyloid deposits
  - Monoclonal antibodies targeting precursor proteins or amyloid fibrils to facilitate immune-mediated clearance (ATTR, AL amyloidosis, Alzheimer disease).
  - Modulators of the proteostasis system, with mitigation of off-target effects.
  - CRISPR–Cas9 gene-editing technologies for one-time interventions (ATTR).
- Determine the effects and indications of non-amyloid-specific therapies (ATTR, AL amyloidosis, Alzheimer disease).
- Develop criteria to monitor disease progression and response to treatment (ATTR).
- Evaluate medin as a primary therapeutic target.

misfolded α-synuclein contributes to central autonomic failure and might also affect platelets and the peripheral vasculature. α-Synuclein is expressed by multiple cell types, including neurons and blood cells, and can adopt distinct conformational states coexisting in a heterogeneous conformational ensemble, with the monomeric protein being intrinsically disordered, and higher-order assemblies forming in specific conditions[145].

In Parkinson disease and related α-synucleinopathies, post-translational modification of α-synuclein and templated interactions with pre-existing α-synuclein aggregates promote misfolding into oligomers, fibrils and Lewy bodies[145]. Cardiovascular involvement is increasingly recognized, particularly through autonomic dysfunction, orthostatic hypotension and abnormal vascular regulation[146]. Parkinson disease is characterized by blood–brain barrier dysfunction, including increased permeability, aggregated α-synuclein-mediated altered expression of tight junction proteins in endothelial cells, increased release of pro-inflammatory mediators from endothelial cells and pathological immune cell infiltration through the blood–brain barrier[10,147,148]. In Parkinson disease, aggregated α-synuclein also activates platelets, monocytes and T cells, resulting in an inflammatory response both in the brain and in the periphery, a hallmark of disease progression[10,149]. Additionally, α-synuclein is deposited in endothelial cells, accompanied by intracerebral endothelial degeneration and pathological angiogenesis that are followed by cerebral vascular regression in late stages of disease[147,150]. Specific gene variants, such as E46K in *SNCA* (which encodes α-synuclein), G2385R in *LRRK2* or variants in *GBA1*, are associated with autonomic dysfunction in Parkinson disease[151].

Although associations between Parkinson disease and coronary artery disease have been reported in cohort studies, shared biases related to age, frailty, the presence of inflammation, medication exposure and patient surveillance complicate interpretations of causality[152]. Overall, the most robust cardiovascular evidence for α-synuclein-related disorders supports neurogenic dysregulation (orthostatic hypotension, baroreflex or vasoconstriction reserve dysfunction and supine hypertension)[146]. By contrast, data for direct α-synuclein-mediated vascular proteotoxicity or α-synuclein-deposition-driven vasculopathy are comparatively limited and often indirect. Consequently, these mechanisms require tissue-level validation and prospective linkage to vascular end points. Therefore, the most robust cardiovascular signal in α-synucleinopathies is dysautonomia, whereas the direct contribution to macrovascular disease remains hypothesis-generating rather than established.

Other causes of protein misfolding diseases. Protein misfolding or aggregation has been observed in failing human hearts after ischaemic injury or cardiac-load-dependent heart diseases such as hypertension. Other, less common PMDs (such as SAA or β2-microglobulin (Aβ2M) amyloidoses) can also affect the heart[153]. Aβ2M amyloidosis is an exclusive complication of long-term dialysis and has become less common in the past three decades partly due to improved techniques using high-flow membranes since 1997 (ref. 154). Aβ2M deposition occurs in small-sized and medium-sized vessels in the myocardium and perivascular fibrous tissue, endocardium, subendocardium, myocardial interstitium, atrioventricular node, aortic and mitral valves, and synovium, as well as in intestinal vessels, which can result in intestinal ischaemia, infarction and perforation[154]. Complications of severe cardiac Aβ2M deposition include atrial dilatation and heart failure[154].

Desmin-related cardiomyopathy is an inherited condition caused by variants in *DES* (which encodes desmin) or in genes related to desmin quality control such as *CRYAB* (which encodes the chaperone α-crystallin B chain, a key mediator of desmin folding). Misfolded desmin can drive the formation of toxic oligomeric species and protein aggregates, contributing to cardiomyocyte dysfunction and cardiac pathology[155]. In addition, the deposition of amyloid derived from atrial natriuretic peptide causes isolated atrial amyloidosis, which is most commonly found in patients with valvular heart disease, increasing the risk of atrial fibrillation[156,157].

Other amyloidogenic precursor proteins prone to misfolding and deposition in vascular sites have been reported but their clinical relevance is under investigation. In almost all individuals aged >50 years, apolipoprotein A-I amyloid deposits are detected in the aorta[158]. When apolipoprotein A-I molecules dissociate from their lipid cargo or carry destabilizing sequence variants, the native α-helical structure loosens, allowing the proteins to misfold into β-sheet fibrils. Several apolipoprotein-derived amyloid deposits have been observed within the subendothelial regions of atherosclerotic plaques and in association with calcified aortic valve lesions[27,159]. The clinical relevance of these findings remains to be elucidated.

Protein misfolding has emerged as a contributing factor in metabolic and vascular diseases such as atherosclerosis and type 2 diabetes[160,161]. Oxidized LDL has amyloid-like properties[162] and can activate platelets, thereby promoting thrombus formation[163]. Similarly, hyperglycaemia induces glycation of haemoglobin and albumin, conferring amyloid characteristics that might contribute to platelet hyperreactivity and increased thrombotic risk[164,165]. Pancreatic β-cell dysfunction and apoptosis in patients with type 2 diabetes might be mediated by the accumulation of misfolded proteins in the mitochondria of pancreatic islets[164,166]. Collectively, these observations suggest that vascular amyloid and amyloid-like deposits are far more widespread than clinically apparent amyloidosis but their contribution to vascular disease and thrombosis remains incompletely defined.

Presentation, diagnosis and prognosis

General characteristics of cardiac amyloidosis

Cardiac amyloidosis typically presents as cardiomyopathy, restrictive diastolic filling patterns, elevated filling pressures and preserved radial contractility. Indeed, left ventricular ejection fraction is typically preserved until late stages of cardiac amyloidosis, but systolic function is disproportionately affected in the longitudinal rather than the radial axis[167]. This reduction in longitudinal strain typically spares the apex, giving a 'cherry-on-top pattern' on parametric strain maps[168–170]. Key imaging hallmarks also include left ventricular wall thickening with preserved cavity size, a restrictive filling pattern and late gadolinium subendocardial enhancement[171]. The most critical step in the diagnosis of cardiac amyloidosis remains clinical suspicion, which should prompt immediate action for rapid diagnosis[167,170,172–175]. Suspicion should be high in any patient presenting with heart failure that is unexplained or disproportionate to clinical findings, particularly when accompanied by persistently elevated and discordant plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Transthyretin amyloidosis

Cardiac involvement. Wild-type ATTR primarily affects the heart, whereas cardiac involvement in hereditary ATTR is variable and largely determined by the specific *TTR* variant. Clinically, wild-type ATTR typically presents in older men with heart failure with preserved ejection

Table 2 | Diagnosis of cardiovascular involvement in protein misfolding diseases

Disease	Cardiac		Vascular		Soft-tissue, gastrointestinal, neurological features
	Symptoms, clinical manifestations	Laboratory and imaging hallmarks	Symptoms, clinical manifestations	Laboratory and imaging hallmarks	
Wild-type ATTR	Bradycardia, HF, palpitations, syncope	ECG: AF, AV block, pseudoinfarct Q-waves, low-voltage ECG[171] TTE: LV hypertrophy, apical sparing[171], HFpEF, restrictive cardiomyopathy[171], biatrial enlargement, AS[309], pericardial effusion[174] CMR: non-ischaemic subendocardial LGE, and ↑ ECV, T1, T2 (refs. 171,310) Bone scintigraphy: grade 2–3 tracer uptake[171] Laboratory: ↑ NT-proBNP and troponin levels[171]	OH (non-neurogenic, late stage)[88], exertional or bradyarrhythmic syncope[174,311]	Low peripheral BP[191]	Bilateral CTS, lumbar spinal stenosis, biceps tendon rupture[171,312]
Hereditary ATTR	Bradycardia, early-onset HF, palpitations, syncope	Same as for wild-type ATTR (cardiomyopathy phenotype predominant)	Neurogenic OH[88], syncope[174]	Low peripheral BP[191]	Phenotypic variability (*TTR* gene variant dependent), including cachexia, diarrhoea, constipation, frequent sensory and autonomic neuropathy, vitreous opacities[174]
Immunoglobulin light chain amyloidosis	Rapidly progressive HF, pleural effusions, syncope, jugular venous distension, hepatomegaly, peripheral oedema	ECG: low voltage (more frequent than in ATTR)[171] TTE: LV hypertrophy, biatrial enlargement (not as great as in ATTR), pericardial effusion[167] CMR: non-ischaemic subendocardial or transmural LGE, and ↑ ECV, T1, T2 (ref. 171)	OH, syncope[105,313]	Low peripheral BP[105], abnormal reactive vasodilatation to ischaemia and sympathetic stimulation[198], haemorrhagic and peripheral thrombotic events[74]	Macroglossia, periorbital purpura, nephrotic syndrome, autonomic and sensory neuropathy, weight loss, diarrhoea[175]
Amyloid-β-associated diseases (AD and CAA)	Frequent CV comorbidities, including CAD, CV risk factors and HF[115]	Limited evidence of validated hallmarks for clinical use	Co-existence of CAA (vascular deposition of $A\beta_{40}$) with accelerated cognitive impairment and intracerebral haemorrhage[8]	Accelerated atherosclerosis, characteristic MRI and CSF findings in CAA[314]	Progressive cognitive decline, dysautonomia, gastrointestinal dysmotility, cachexia, weight loss
α-Synuclein-related diseases (such as Parkinson disease)	Exercise intolerance[146], frequent arrhythmias[146], palpitations	ECG: sinus arrhythmia, QTc prolongation PET: markedly reduced ^{123}I-MIBG and ^{18}F-FDA uptake[146]	OH, impaired baroreflex and vasoconstriction[146], frequent co-existent stroke[212]	Low peripheral BP, ↓ heart rate variability[146]	Motor parkinsonism, REM sleep behaviour disorder, constipation, broad autonomic neuropathy[315]

^{18}F-FDA, fluorine-18 fluorodopamine; ^{123}I-MIBG, iodine-123 metaiodobenzylguanidine; $A\beta_{40}$, amyloid-β_{40}; AD, Alzheimer disease; AF, atrial fibrillation; AS, aortic stenosis; ATTR, transthyretin amyloidosis; AV, atrioventricular; BP, blood pressure; CAA, cerebral amyloid angiopathy; CAD, coronary artery disease; CMR, cardiac MRI; CSF, cerebrospinal fluid; CTS, carpal tunnel syndrome; CV, cardiovascular; ECG, electrocardiography; ECV, extracellular volume; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OH, orthostatic hypotension; PET, positron emission tomography; REM, rapid eye movement; TTE, transthoracic echocardiography.

fraction or low-flow aortic stenosis, carpal tunnel syndrome and biceps tendon rupture. By contrast, *TTR* variants that cause hereditary ATTR produce more heterogeneous phenotypes with varying degrees of cardiomyopathy and neuropathy[6]. Compared with AL amyloidosis, ATTR-related cardiomyopathy tends to have a slower trajectory and lower early mortality but substantial long-term heart failure burden. Disease mechanisms, therapeutic targets and available therapies have been reviewed elsewhere[176] (Tables 2 and 3, and Supplementary Text).

Advances in non-invasive diagnosis and the availability of disease-modifying therapies for ATTR have reshaped practice and given impetus to screening[171]. However, our understanding of the epidemiology of cardiac involvement in ATTR derives largely from administrative datasets and patient registries, in which subclinical disease can be missed[177]. Non-invasive diagnosis is highly valuable, but important areas of uncertainty should be considered. Perugini scale grade 1 findings on bone scintigraphy are non-specific and should not be interpreted as confirmatory evidence of ATTR cardiomyopathy[178]. In addition, monoclonal gammopathy is common in older adults and can coexist with ATTR, complicating attribution and mandating careful haematological evaluation to exclude AL amyloidosis[179]. In such cases, a low threshold for tissue typing (or repeat imaging or biomarker integration at follow-up) is warranted to avoid misclassification.

ATTR and aortic stenosis frequently coexist, and shared age-related decline in proteostasis and valvular or interstitial remodelling provide mechanistic plausibility for bidirectional reinforcement[180]. Amyloid deposition in stenotic aortic valves has been described and

Table 3 | Treatment of cardiovascular involvement in protein misfolding diseases

Disease	Approved disease-specific treatment	Residual risk after optimal treatment	Clinical trial outcomes
Wild-type ATTR	Acoramidis (transthyretin stabilizer)[316]	Death or CV hospitalization 35.9% (over 30 months)[317]	HR for the composite of death or CV hospitalization 0.64 (95% CI 0.50–0.83)[317]
	Tafamidis (transthyretin stabilizer)[237]	Death 39% (median 43 months; 54% alive at 65 months)[237]	HR for death 0.70 (95% CI 0.51–0.96); RR for CV hospitalizations 0.68 (95% CI 0.56–0.81)[239]
	Vutrisiran (RNA silencer: siRNA)[318]	Death or CV events 38.5% (over 42 months)[318]	HR for death and CV events 0.67 (95% CI 0.51–0.90)[318]
Hereditary ATTR	Polyneuropathy: eplontersen (ASO)[319], inotersen (ASO)[319], patisiran (siRNA)[320] Polyneuropathy and cardiac involvement: vutrisiran (siRNA)[321]	Vutrisiran: death or CV events 38.5% (over 42 months)[318]	Vutrisiran: HR for death and CV events 0.92 (95% CI 0.49–1.72)[318]
Immunoglobulin light chain amyloidosis	Daratumumab (anti-CD38 mAb)[234] Bortezomib (proteasome inhibitor)[322] Lenalidomide (immunomodulatory drug)[323]	50% rate of complete response with optimal combination of any currently available treatments[95] Bortezomib: median survival 56 months[324] Lenalidomide: median survival 24 months[323]	Daratumumab: composite HR 0.58 (95% CI 0.36–0.93), mortality at 24 months: 12.5% (no benefit in overall survival)[234] Bortezomib: HR for death 0.50 (95% CI 0.27–0.90), mortality 32% at 50 months[322]
Amyloid-β-associated diseases (AD and CAA)	In amyloid-β-related extracerebral CV injury without cerebral disease, repurposing of amyloid-specific treatments could be of value mAbs for AD: aducanumab (binds to soluble amyloid-β aggregates and insoluble fibrils)[325], donanemab (binds to insoluble, modified N-terminal truncated form of amyloid-β)[326], lecanemab (binds to amyloid-β protofibrils, preventing plaque formation)[327] Inhibitors of precursor synthesis for AD[326]: BACE1 inhibitors[328], γ-secretase inhibitors[329]	Despite slowing the progression of cognitive impairment, the clinical relevance of anti-amyloid-β mAbs in CVD is unknown	No published data
α-Synuclein-related diseases (such as Parkinson disease)	No specific treatment for CV involvement (lack of targets)	Autonomic dysfunction during exercise is not improved by treatment for Parkinson disease[330]	No published data

Benchmark outcomes are provided where available. Clinical trials differ in inclusion criteria, disease stage, background therapy, follow-up duration and primary end points. Numeric estimates are presented to contextualize residual risk within each study and should not be used for indirect efficacy ranking across therapies. AD, Alzheimer disease; ASO, antisense oligonucleotide; ATTR, transthyretin amyloidosis; BACE1, β-secretase 1; CAA, cerebral amyloid angiopathy; CV, cardiovascular; CVD, cardiovascular disease; mAb, monoclonal antibody; RR, risk ratio; siRNA, small interfering RNA.

can worsen stenosis by triggering inflammation, myofibroblast proliferation, endothelial cell dysfunction and valve thickening, resulting in cardiac pressure overload[181,182]. In combination with local inflammation and oxidative stress, pressure overload can directly facilitate transthyretin amyloid deposition in the myocardium and valves[183]. However, the available clinical evidence is observational and susceptible to selection and detection bias, thus directionality and effect size remain uncertain. Therefore, we frame the relationship as a plausible synergy that warrants prospective evaluation with standardized assessment for amyloid deposition in patient cohorts of aortic stenosis and vice versa. In addition to aortic stenosis, risk scores and phenomaps for ATTR diagnosis have been developed[184,185], but external validation of their clinical applicability is pending.

Artificial intelligence-based tools could be integrated into amyloidosis screening pathways to triage patients with heart failure, left ventricular hypertrophy, aortic stenosis or carpal tunnel syndrome into targeted confirmatory testing (bone scintigraphy or cardiac MRI (CMR)). This approach could accelerate exclusion of AL amyloidosis when monoclonal gammopathy is present, and enable early initiation of disease-modifying therapy and disease subtype-specific management. A novel machine learning random forest-based model, trained on data from 1,071 patients with wild-type ATTR and 1,071 control patients with non-amyloid heart failure (validated in four cohorts of approximately 58,000 patients), identified those with heart failure at risk of ATTR cardiomyopathy with high accuracy (area under the receiver operating characteristic curve (AUROC) 0.75–0.96)[186]. This tool could provide a systematic framework to screen for wild-type ATTR in patients with heart failure. In a study using electrocardiographic and echocardiographic data from two cohorts (n = 984 and n = 806), deep-learning-derived scores for discriminating cardiac ATTR diverged between patients and matched controls up to 3 years before clinical diagnosis[187]. A locally deployable, image-based artificial intelligence–electrocardiography model identified ATTR cardiomyopathy with consistent discrimination across multinational cohorts (AUROC 0.76–0.91), supporting the potential of this approach as a scalable tool to prioritize patients for further confirmatory evaluation[188]. These findings constitute important proof of principle, suggesting that artificial intelligence-based tools can detect a latent disease signature before overt clinical recognition in selected patient populations. In practical terms, such artificial intelligence algorithms could be used to pre-screen patients with hypertrophic or heart failure with preserved ejection fraction-like phenotypes and triage them for bone scintigraphy or CMR. However, the clinical implications should not be overstated. Case-enriched derivation cohorts can inflate apparent performance

of artificial intelligence algorithms, and whether these algorithms retain discrimination, calibration and acceptable false-positive rates in low-prevalence, real-world populations or across vendors, acquisition protocols, and health-care systems, remains uncertain. The true value of these tools will depend less on retrospective accuracy than on whether prospective implementation improves diagnostic timeliness, resource allocation and patient outcomes without creating excessive downstream testing.

Vascular involvement. Patients with cardiac ATTR can have increased vessel stiffness, compromised autonomic regulation and a prothrombotic condition (Table 1), although the evidence remains limited[88,189,190]. Patients with wild-type ATTR have a distinct peripheral vascular profile, characterized by lower aortic and brachial blood pressure, but no difference in markers of arterial stiffening compared with patients with systemic AL amyloidosis or cardiac amyloidosis or with healthy individuals[191]. This vascular pattern seems to be unique to wild-type ATTR. Therefore, despite the expected infiltration of amyloid fibres into the vascular wall, no clinically meaningful effect on arterial stiffness has been proven in wild-type ATTR[191]. However, hypotension can mask vascular injury and accelerated vascular ageing in these patients; therefore, whether arterial stiffening becomes apparent in more advanced stages of wild-type ATTR remains unclear[192].

AL amyloidosis

Cardiac involvement. AL amyloidosis is a major cause of cardiac involvement in PMDs[95]. Diagnosis requires the demonstration and typing of amyloid deposits in tissue biopsy samples[193]. The presence and severity of cardiac involvement at presentation drive prognosis but effective immunotherapy and chemotherapy regimens have improved survival[95]. Cardiac involvement in AL amyloidosis has been comprehensively discussed elsewhere[95] (Tables 2 and 3, Supplementary Text, and Supplementary Table 1).

Vascular involvement. In AL amyloidosis, the clinical ramifications of vascular involvement are extensive and often overlap with other systemic signs of amyloidosis (Table 2). Vascular amyloid deposits and FLC toxicity can alter vascular function, which in turn affects organ function and underlies some of the clinical manifestations. The histological hallmark of vascular involvement in AL amyloidosis is intramural amyloid deposition in small vessels, with endothelial injury from toxic FLC[14] (Table 1). In a study of autopsy specimens and hearts explanted during transplantation, 97% of patients with AL amyloidosis had perivascular amyloid infiltrating the intima, media or adventitia of the small epicardial coronary arteries[104]. However, complete obstruction of intramural coronary arteries has only been described as a rare complication in AL amyloidosis at autopsy or in explanted hearts[104,194,195].

The macrovascular phenotype of AL amyloidosis remains under investigation. Vascular autonomic dysfunction can culminate in orthostatic hypotension and low resting blood pressure[105]. These established complications of cardiac AL amyloidosis are progressively debilitating, associated with intolerance to standard treatments for heart failure and linked to worse prognosis (Supplementary Table 1). A small study of 59 patients with AL amyloidosis showed increased carotid intima–media thickness and decreased brachial artery flow-mediated dilatation (FMD) compared with 17 age-matched healthy control individuals[196]. However, a subsequent larger study of 170 patients with AL amyloidosis (115 in the derivation cohort and 55 in the validation cohort) and control individuals without amyloidosis matched for age, sex and CVD risk factors did not confirm increased carotid atherosclerosis burden in these patients[191,197]. Interestingly, paradoxically increased FMD was reported in the larger study, which was similar to the FMD in control groups with a lower cardiovascular risk[197]. Patients with AL amyloidosis had increased nitric oxide marker levels and FMD that correlated with augmented sustained vasodilatation after sympathetic stimulation[197], suggesting that paradoxical reactive vasodilatation might be driven by vascular autonomic dysfunction, a common mediating mechanism for hypotension in AL amyloidosis. Importantly, in this study, an FMD ≥4.5% was associated with a fourfold increase in the risk of early death (at 6 months of follow-up) and correctly classified both these patients at high risk and patients at lower risk who survived until the end of follow-up (median 45 months)[197]. FMD has also been linked with sustained peripheral and aortic blood pressure reduction in response to sympathetic stimulation by cold pressor test (in contrast to vasoconstriction and blood pressure increase response in control individuals), which in turn was correlated with poor survival[198]. Notably, reactive vasodilatation assessed by FMD or cold pressor test was associated with worse response to haematological treatment[197,198]. These data indicate that patients with AL amyloidosis at high risk for death do not show vasoconstriction in response to sympathetic activation, whereas a poor haematological response to treatment associates with further deterioration of blood pressure, probably due to the continuous production of toxic IgLCs and amyloids. This paradoxical dilatation in response to sympathetic stress reflects failure of normal vasoconstrictive reserve, contributing to hypotension, syncope and limited tolerance to heart failure therapies. Together, these observations support AL amyloidosis as a systemic vasculopathy characterized by microvascular obstruction and endothelial toxicity, overlaid by autonomic macrovascular dysfunction that produces orthostatic hypotension and paradoxical vasodilatation.

Amyloid-β-mediated diseases

Cardiac involvement. CAA is defined by $A\beta_{40}$ deposition in leptomeningeal and cortical small vessels, and frequently coexists with Alzheimer disease[199]. In Alzheimer disease, echocardiographic and tissue studies suggest subclinical diastolic dysfunction with evidence of intramyocardial $A\beta_{40}$ and $A\beta_{42}$ deposition, respectively[124,200]. The extracerebral circulating level of amyloid-β increases with age and has been detected in the myocardium, with its clinical relevance under active study. Crucially, although the central nervous system is the primary source of amyloid-β, the cardiovascular system is not merely a passive sink. The heart itself (via cardiomyocyte expression of amyloid-β precursor protein and β-secretase 1 (BACE1))[8,115,125,201] and activated platelets[61,65] contribute substantially to the local and systemic proteotoxic load of amyloid-β. High circulating $A\beta_{40}$ levels are independently associated with adverse cardiovascular outcomes, including death, in patients with stable coronary artery disease, acute coronary syndrome (ACS) or heart failure, improving risk stratification over guideline-recommended scores[125,202,203]. Whether circulating $A\beta_{40}$ primarily reflects underlying vascular injury or actively drives it is uncertain, and current data suggest a bidirectional relationship. Although experimental models demonstrate direct proteotoxicity of amyloid-β, the epidemiological evidence linking extracerebral amyloid-β levels to systemic CVD requires rigorous critical appraisal. Although $A\beta_{40}$ acts as a potent and independent prognostic biomarker, further investigations, including Mendelian randomization studies, are necessary to definitively disentangle its active causal role from confounding factors such as age-related renal decline or general vascular inflammation.

Vascular involvement. Plasma levels of $A\beta_{40}$ are independently associated with measured and estimated aortic stiffness and its longitudinal changes, irrespective of the presence of Alzheimer disease[203]. $A\beta_{40}$ is also a surrogate for vascular ageing and associated with the presence, extent and progression of atherosclerosis with vulnerable carotid atherosclerotic plaque[204–206]. In patients with chronic coronary syndrome and ACS, increased plasma levels of $A\beta_{40}$ were consistently and independently associated with major adverse cardiovascular events, including relapse of ACS, suggesting that $A\beta_{40}$ metabolism might promote atherosclerotic plaque rupture[202,203] (Table 1).

α-Synucleinopathies

In α-synucleinopathies, such as Parkinson disease, cardiovascular dysautonomia is common and associated with poor outcomes[207,208] (Table 2). Indeed, autonomic nervous system dysregulation leads to orthostatic hypotension, occurring in up to one-third of patients with Parkinson disease[209], coexisting with supine hypertension and a non-dipping pattern[210,211]. Patients with Parkinson disease also exhibit an insufficient blood pressure and heart rate response during exercise, making disease management particularly challenging[210]. Additionally, these patients have a higher risk of heart failure and ventricular tachyarrhythmias than age-matched and sex-matched control individuals[212] but the mechanisms underlying these associations are not fully understood (Fig. 2).

Although α-synuclein deposits hold promise as a biomarker for neurogenic cardiovascular dysfunction, current evidence is largely associative. Establishing the definitive role of α-synuclein deposits as a causative systemic driver requires careful methodological consideration and further validation in human cohorts to rule out confounding and reverse causality.

Emerging biomarkers

Several diagnostic and prognostic biomarkers have been established for the diagnosis and management of cardiovascular involvement in PMDs, and many have been incorporated into staging systems and risk scores (Supplementary Table 2). Useful clinical tools in this context include measurement of NT-proBNP, BNP and cardiac troponin levels in plasma, immunofixation, dFLC (the difference between the concentration of involved FLCs and uninvolved FLCs), direct identification of FLCs using mass spectrometry, global longitudinal strain in speckle-tracking echocardiography, and T1 mapping or extracellular volume on CMR; indeed, use of these tools is recommended in expert consensus statements and guidelines. Notably, currently recommended biomarkers mainly pertain to AL amyloidosis and ATTR. Emerging blood-borne biomarkers under investigation include $A\beta_{40}$ and $A\beta_{42}$, circulating transthyretin, growth differentiation factor 15 (GDF15), soluble IL-1 receptor-like 1 (also known as suppression of tumorigenesis 2 (sST2)), von Willebrand factor (vWF), retinol-binding protein 4, osteopontin, osteoprotegerin, transthyretin fibrils and aggregates, and noradrenaline. Other emerging, non-molecular biomarkers and tests for PMDs include heart rate variability, FMD, blood pressure patterns, blood pressure after cold pressor test, the return time of reflected waves (a marker of arterial stiffness), T2 mapping in CMR, left atrial, right ventricular free wall and right atrial strain on speckle-tracking echocardiography, and transcranial sonography.

Many emerging biomarkers under investigation (such as GDF15, sST2 and vWF) are biologically plausible risk integrators but are not specific to proteotoxic injury and primarily reflect downstream endothelial activation, inflammation and haemodynamic stress. Such biomarkers should be flagged as 'non-specific' and used to refine risk stratification, rather than as direct readouts of proteotoxic load. Research on these emerging biomarkers in PMDs should explore their potential incremental diagnostic and prognostic utility beyond standard-of-care in contemporary cohorts to improve risk stratification and assessment of response to treatment (Supplementary Text and Supplementary Table 2).

Artificial intelligence

Artificial intelligence-based methods, particularly deep learning and neural network-based approaches, now allow for refined diagnosis and risk stratification across a broad spectrum of CVDs, fostering a paradigm shift in the diagnosis and thus prognosis of PMDs. Several artificial intelligence-based models, such as machine learning models, are currently available for the early detection of cardiac amyloidosis, leveraging data from electrocardiography, echocardiography, CMR, CT and routine laboratory tests[213–219] (Supplementary Table 3). These algorithms have demonstrated robust diagnostic accuracy, frequently achieving AUROC values >0.90. In addition, they can detect disease years before its clinical manifestation and accurately differentiate cardiac amyloidosis from phenocopies such as aortic stenosis and hypertrophic cardiomyopathy.

For example, a three-stage machine learning algorithm leveraging CMR and demographic data trained on data from 400 participants sequentially differentiated healthy individuals from patients with hypertrophic cardiomyopathy or ATTR or AL amyloidosis, then differentiated hypertrophic cardiomyopathy from amyloidosis, and finally AL amyloidosis from ATTR[218]. In another study, based on 12-lead electrocardiographic data, a neural network was trained and validated on 4,995 participants to predict cardiac amyloidosis, achieving an AUROC of 0.91 (95% CI 0.90–0.93)[213]. This concept was developed one step further by introducing a convolutional neural network to differentiate between cardiac amyloidosis and phenotypic controls using a single apical four-chamber video clip[217]. Trained and externally validated in 5,331 study participants, the algorithm achieved an AUROC of 0.93 to detect cardiac amyloidosis, with sensitivity exceeding 80%, irrespective of the cardiac amyloidosis subtype present[217]. Another deep-learning model applied to 5,776 patients provided a sensitivity of 86.6–92.3% and a specificity of 85.3–87.9% during external validation for the detection of cardiac amyloidosis following echocardiography[216].

Despite these promising findings, a crucial unmet need remains in the screening landscape. Current artificial intelligence models, such as machine learning models, cannot screen patients presenting solely with extracardiac 'red flag' manifestations such as carpal tunnel syndrome, lumbar spinal stenosis or spontaneous biceps tendon rupture, who are at high risk of subsequently developing amyloid cardiomyopathy. However, emerging proof-of-concept data from conference abstracts and preprints suggest that novel algorithms are beginning to bridge this gap[220–222]. By utilizing natural language processing and machine learning tools to integrate early systemic, orthopaedic and neurological signals from unstructured electronic health records, these early-stage models aim to trigger targeted cardiovascular assessment well before overt symptoms of structural heart disease or heart failure emerge, opening opportunities for early therapeutic intervention.

Challenges and knowledge gaps

Vascular autonomic dysfunction is a hallmark of vascular involvement in AL amyloidosis but simply measuring peripheral systolic blood pressure and testing for orthostatic hypotension does not fully capture

associated risk. Evidence suggests that dynamic responses to reactive hyperaemia and sympathetic stimuli by cold pressor test in estimated aortic blood pressure and brachial diameter can confer additive value beyond measurement of peripheral blood pressure[198]. Although these markers of vascular function can follow haematological responses[198] and are associated with all-cause mortality[197] independently of the severity of cardiac involvement, their clinical utility as prognostic or therapeutic biomarkers in AL amyloidosis merits further validation. Vascular dysfunction in ATTR is less evident than in AL amyloidosis, and measures of vascular or haemodynamic markers in these patients might be similar to age-specific and sex-specific reference values[197]. Therefore, diagnosis of ATTR is challenging. Future vascular risk scores for PMDs might integrate autonomic metrics (such as severity of orthostatic hypotension and blood pressure variability), functional vascular tests (such as cold pressor test, FMD and pulse wave velocity) and biomarkers of endothelial injury (such as GDF15 and vWF) but such tools will require prospective validation.

Treatment and management

Current clinical approach to PMDs

Guideline recommendations for the clinical management of AL amyloidosis and ATTR have been updated in the past 3 years[95,223–226]. Transthyretin stabilizers (acoramidis and tafamidis) and the mRNA silencer vutrisiran are approved by the EMA and the FDA for the treatment of cardiac ATTR, and have received a class IA recommendation for patients with variant or wild-type cardiac ATTR with NYHA class I–III to reduce the progression of symptoms and the risk of hospitalizations for cardiovascular causes and all-cause death[226]. All these agents were associated with structural and functional left ventricular changes that supported the observed benefit of reduced mortality and cardiovascular events[227–229]. In a rapidly evolving landscape, another mRNA silencing agent, eplontersen, was evaluated in the phase III, double-blind, randomized controlled CARDIO-TTRansform trial, which included a broad population of patients with ATTR cardiomyopathy with NYHA class I–III (n = 1,432) and uniquely allowed unrestricted background transthyretin-stabilizer therapy[230]. Despite a rapid and sustained suppression of circulating transthyretin levels, the CARDIO-TTRansform trial did not establish a significant benefit of eplontersen for the primary composite end point of cardiovascular mortality and recurrent cardiovascular events compared with placebo[230]. By contrast, several secondary outcomes, including the 6-min walking distance, the Kansas City Cardiomyopathy Questionnaire and all-cause mortality, significantly favoured eplontersen. Of note, a strong interaction between baseline use of a transthyretin stabilizer and eplontersen treatment effect was found for the primary end point. In this context, a prespecified analysis showed that, among patients not receiving a transthyretin stabilizer at baseline, eplontersen was associated with fewer primary end point events and recurrent cardiovascular events and mitigated the decline in the Kansas City Cardiomyopathy Questionnaire and 6-min walking distance compared with placebo[231]. The significant results across all the studied end points in the monotherapy cohort (no transthyretin stabilizer at baseline) indicate that eplontersen provides clinically meaningful benefits but not when combined with a stabilizer. Conversely, treatment effect estimates for vutrisiran therapy on clinical outcomes in the HELIOS-B trial[232] were consistent across baseline tafamidis strata, with no significant interaction according to baseline tafamidis use but with reduced effect size and wide confidence intervals noted in those receiving transthyretin stabilizers at baseline compared with vutrisiran monotherapy. Differences in trial design and patient populations probably influenced these contrasting interaction results in CARDIO-TTRansform and HELIOS-B. HELIOS-B featured a lower rate of baseline use of tafamidis (40.0%, with a median previous duration of treatment of 11 months) and restricted post-randomization drop-in, limiting subsequent initiation of tafamidis to approximately 20% of baseline non-users events[227]. A meta-analysis pooling data from both trials (n = 2,086) confirmed an overall 20% reduction in all-cause mortality and recurrent cardiovascular events with *TTR* mRNA silencer therapies. Importantly, this pooled analysis established substantial treatment heterogeneity by baseline use of transthyretin stabilizers, demonstrating considerable efficacy in patients receiving *TTR* mRNA silencer monotherapy (rate ratio 0.69) and no incremental clinical benefit when added to background therapy with transthyretin stabilizers (rate ratio 0.97)[233]. In aggregate, these data underscore the need for future prospective studies to explore whether specific patient, disease or agent characteristics affect the outcomes with combination therapies in patients with ATTR cardiomyopathy.

Regarding AL amyloidosis, combination therapy with the monoclonal antibody daratumumab and the proteasome inhibitor bortezomib is an approved treatment for patients with cardiac involvement[234]. Furthermore, promising results for cardiac AL amyloidosis treatment have been reported with drugs that target TNF receptor superfamily member 17 (also known as B cell maturation protein) on the plasma cell surface[235,236]. To date, no drugs have been approved for the management of amyloid-β-related cardiovascular involvement in neurodegenerative diseases. Repurposing of therapies under investigation or approved for Alzheimer disease, and off-target effects of CVD therapies on $A\beta_{40}$, seem to be the most promising approaches (see the next section on 'targeting cardiac involvement'). Similarly, autonomic dysfunction in α-synucleinopathies, such as Parkinson disease, could be managed with supportive therapy targeting symptoms but no amyloid-specific therapy exists. More details on strategies to mitigate cardiovascular impairment and supportive care in PMDs can be found in Tables 3 and 4 and in the Supplementary Text.

Targeting cardiac involvement

Although transthyretin stabilization with tafamidis has reshaped the natural history of cardiac ATTR, substantial residual risk remains (Table 3). In a contemporary multicentre cohort, 39% of 624 patients treated with tafamidis died during follow-up (median 43 months)[237], underscoring that treatment frequently slows disease progression rather than restoring normal cardiovascular physiology. Longitudinal data demonstrated that treatment with tafamidis was associated with reduction of arterial stiffening in 24 patients with wild-type ATTR cardiomyopathy compared with 30 control individuals aged >70 years[91]. These findings suggest that transthyretin stabilizers can partially reverse accelerated vascular ageing, improve ventricular–arterial coupling and enable recovery of the proteostasis network[91].

Cardiac dysfunction often persists or progresses when therapy is started late in the disease process, and neurological deficits in ATTR polyneuropathy likewise often remain only partially reversible despite gene-silencing therapy[238,239]. These observations support a stage-dependent interpretation of treatment effect. Stabilization or suppression of precursor proteins is most effective before extensive fibril burden, fibrosis and microvascular injury become entrenched. Accordingly, currently available transthyretin-directed therapies should be viewed as disease-modifying, rather than disease-reversing, therapies, and future strategies will probably need to combine early diagnosis with approaches that actively clear deposited amyloid or

Table 4 | Ongoing randomized clinical trials of amyloid-specific therapies with effects on cardiovascular involvement

Drug		Clinical trial					
Name	**Mechanism of action**	**Name (refs.)**	**Phase**	**Cohort**	**Duration**	**Primary end points**	**Secondary end points**
Gene editors and mRNA silencers							
NTLA-2001 (Nex-Z)	Liver-targeted CRISPR–Cas9 in vivo gene editing (*TTR* knockout)	MAGNITUDE[281]	III	1,200 patients with cardiac ATTR	Event-driven 18 months to ~4 years	Death and hospitalizations for HF	Levels of biomarkers, echocardiography, QoL by KCCQ-OS, safety, long-term durability assessed by serum TTR levels
Nucresiran (ALN-TTRSC04)	GalNAc-conjugated, liver-targeted siRNA targeting *TTR* mRNA	TRITON-CM[331]	III	1,200 patients with cardiac ATTR	Event-driven 24 months	Death and recurrent CV events	Death, CV events, recurrent CV events, QoL by KCCQ-OS
Protein depleters							
ALXN2220 (NI006)	Anti-transthyretin fibril mAb	Deple-TTR[279,332]	III	>1,000 patients with cardiac ATTR	Event-driven 18 months to 4 years	Death and recurrent CV events	QoL by KCCQ-OS, 6MWD, time to all-cause death, time to CV-related death, total CV events
Coramitug (NNC6019-0001)	Anti-transthyretin fibril mAb	CLEOPATTRA[333]	III	1,280 patients with cardiac ATTR	~4 years	CV death and recurrent CV events	Hospitalization for HF, plasma level of troponin and NT-proBNP, stroke volume, eGFR, QoL, 6MWD

Populations, end points and duration of follow-up differ between trials; therefore, entries are not intended to support indirect efficacy comparisons. 6MWD, 6-min walking distance; ATTR, transthyretin amyloidosis; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GalNAc, *N*-acetylgalactosamine; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary score; mAb, monoclonal antibody; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QoL, quality of life; siRNA, small interfering RNA; TTR, transthyretin.

restore downstream tissue resilience. Similarly, in cardiac AL amyloidosis, even when a deep haematological response is achieved, patients might have persistent cardiac dysfunction and heart failure due to several factors, including established amyloid deposits that are not removed by anti-plasma cell therapies, λ-isotype amyloidogenic IgLCs and specific features of clonal plasma cells[240,241]. Although rapid and complete suppression of the IgLC clone improves survival, cardiac response might be delayed for 6–24 months and remain incomplete[241]. Some patients experience irreversible organ damage and only partial cardiac recovery, despite a complete haematological response, reflecting the inability of current therapies to clear existing amyloid fibrils[240]. Additional approaches, such as suppression of circulating transthyretin by gene editing, removal of amyloid tissue deposits through monoclonal antibodies in AL amyloidosis and ATTR, induction of macroautophagy or plasma proteostatic mechanisms, enhancing proteostasis, or administration of chaperones, either alone or in combination, could address residual risk (Box 3).

One emerging concept is whether drugs developed to modify amyloid-β metabolism in Alzheimer disease could be repurposed for cardiovascular complications linked to amyloid-β. Monoclonal antibodies, such as aducanumab, donanemab and lecanemab, slow cognitive decline in selected Alzheimer disease populations but the cardiovascular relevance of these drugs is unknown[115,242]. Likewise, BACE1 inhibition reduces levels of $A\beta_{40}$ and $A\beta_{42}$ in the circulation and in cerebrospinal fluid, but whether this reduction translates into vascular benefit is unproven, and clinical trials of neurodegenerative conditions have highlighted potential limitations related to both safety and efficacy[243,244]. Given that BACE1-related pathways are also upregulated in atherosclerotic CVD and heart failure, targeting upstream amyloid-β metabolism remains biologically plausible[125,201]. Additional candidates include amyloid-β-degrading enzymes such as insulin-degrading enzyme and neprilysin[115] (Box 2). Framing these approaches within a common mechanistic taxonomy is useful, but it should not imply that success in one proteinopathy can be assumed to translate to another, given major differences in the precursor proteins, tissue kinetics, and the relative contribution of soluble versus deposited toxic species. Whether reducing the circulating level of amyloid-β improves vascular function, has neutral effects or is even deleterious in some tissues is unknown. Studies with dedicated cardiovascular end points will be required, rather than extrapolating findings from trials of patients with dementia. Novel therapies that reduce circulating quantities of amyloidogenic FLCs have improved prognosis in patients with AL amyloidosis[245] but cardiac involvement profoundly limits overall survival[246].

Targeting vascular involvement

The primary challenge in the management of vascular involvement in PMDs is that, unlike cardiac involvement, its clinical importance is not clearly defined, and neither biomarkers nor scoring systems for diagnosis have been established. Therefore, the clinical effect of therapeutically targeting vascular dysfunction remains unknown (Box 2). The effects of novel drugs, including transthyretin stabilizers and *TTR* mRNA silencers, on vascular dysfunction need further investigation.

The evidence that Alzheimer disease, CAA and extracerebral amyloid-β deposition are interconnected is abundant. However, a gap in the evidence remains relating to drugs that target amyloid-β-related vessel disease and the effect of amyloid-β metabolism-specific therapies on vascular involvement. Existing therapies for α-synucleinopathies include pharmacological interventions for orthostatic hypotension such as fludrocortisone, midodrine and the noradrenaline precursor droxidopa. However, disease-specific medications that target α-synuclein misfolding are still in the investigational phase, including prasinezumab, cinpanemab and Lu AF82422, which are monoclonal antibodies targeting α-synuclein. Therapies for Parkinson disease

have detrimental effects on the cardiovascular system. For example, levodopa can worsen orthostatic hypotension via peripheral vasodilatation and possibly negative inotropic effects, and careful blood pressure monitoring is advised[247]. To date, no specific treatment has been developed for Parkinson disease-related hypotension. Overall, targeting vascular impairment in PMDs might constitute a complementary approach to reducing residual cardiovascular risk, but further research is needed to validate novel biomarkers and to explore the effect of disease-modifying drugs on this system.

Challenges and future directions

Translational challenges

Although age-related decline in proteostasis underlies the emergence of amyloid deposits, fundamental mechanistic questions remain unresolved. First, whether the fibrils seen in ageing hearts spread from a few initial misfolded proteins, or whether each deposit forms independently from separate misfolding events, is unclear. In vitro studies show that, once amyloid seeds are present, the kinetic barrier to fibril growth falls and polymerization accelerates, indicating that seeding might drive later disease stages[22,24,52,159,248]. However, we still know little about how the first nuclei form in living tissues. Second, subtle shifts in aged cardiac microenvironments (for example, ionic strength, matrix elasticity and pH) are likely to favour amyloid formation, providing microdomains primed for nucleation[22,24]. Distinguishing such microenvironments from those present in healthy tissue could inform strategies aimed at delaying or mitigating fibril development. For example, the role of cell types that 'absorb' amyloid, such as macrophages, in local environments remains unexplored[249].

One major challenge is to decipher the spatiotemporal coordination of protein quality control modules. Cardiomyocytes rely on compartmentalized proteostasis at sarcomeres, mitochondria and intercalated discs, but how these modules communicate under stress is poorly defined. The hierarchical interplay between the UPS and autophagy during aggregate clearance is unresolved, including whether these systems operate sequentially or in parallel. Although chaperones, such as HSP70 and HSP90, are upregulated as a counteracting event in response to misfolded proteins, the sustained overactivation of these pathways in chronic disease states can lead to maladaptive remodelling rather than to protection. Similarly, whether augmenting autophagy or proteasomal degradation is universally beneficial remains debatable, as both excessive and insufficient activity can exacerbate cardiac dysfunction[250,251]. Proteostatic resources are not distributed uniformly across cell types. Single-cell analyses suggest that endothelial cells exhibit early proteostatic stress relative to cardiomyocytes, fibroblasts and vascular smooth muscle cells, potentially shaping spatial deposition patterns and microvascular phenotypes[252,253]. This heterogeneity complicates biomarker development and raises the question of whether precision modulation of protein quality control will require cell-type-specific strategies. Key uncertainties include the precise roles of extracellular proteostasis (chaperones), matrix components (such as heparan sulfates) and plasma factors (such as lipids, membrane remnants and proteinases) in amyloid formation, as well as the tissue specificity of intracellular and extracellular aggregation and the contribution of Toll-like receptors to amyloid-related inflammation. Bridging these gaps, through live-tissue proteostasis reporters, spatial proteomics and clinically relevant preclinical models, will be essential to block amyloid formation before the thermodynamic downhill process becomes irreversible.

Studies using aggregation-prone polyglutamine tracts or mutant Cu–Zn superoxide dismutase have revealed compartmentalized protein quality control networks and their dependence on specific cellular contexts[254,255]. Notably, tissue-specific expression studies in *Caenorhabditis elegans* have shown that neuronal misfolded proteins can influence proteostasis in distant tissues, including muscle, suggesting a systemic communication network of protein quality control mechanisms[256]. These findings raise the possibility of systemic communication between protein quality control pathways in cardiac proteinopathies but whether similar circuits exist in mammals remains unknown. Although nematodes lack a contractile heart, transgenic models recapitulate aspects of muscle proteotoxicity, providing a tractable platform for genetic dissection of stress-response pathways[257–259]. However, translating these insights to human myocardium requires cross-species validation and integrated systems-biology approaches[257].

Exophers, membrane-bound structures that extrude cellular waste, have been shown to remove protein aggregates and intact mitochondria from neurons and muscle cells in *C. elegans*[260,261]. These structures facilitate the transfer of toxic components to neighbouring cells with greater proteostatic capacity than the donor cell. In mammals, cardiomyocytes can secrete dysfunctional mitochondria for macrophage-mediated clearance, a process known as heterophagy, which has been linked to reduced inflammasome activation and improved cardiac homeostasis[262,263]. Whether exopher formation is similarly triggered or impaired under pathological conditions, such as ischaemia, and whether it can be harnessed therapeutically, remain open questions.

Preclinical studies

Genetic or dietary interventions that activate branches of the proteostasis network can delay ageing and the development of proteinopathies across diverse organisms[264]. However, preclinical research is now focused on small molecules, biologicals and complex chemical compounds that achieve one or more of the following:

- Bind short sequence motifs to block the aggregation of misfolded proteins.
- Directly suppress the aggregation of misfolded proteins using, for example, monoclonal antibodies.
- Reduce the abundance of misfolded proteins via degradation.
- Activate proteotoxic stress sensors, such as heat shock factor protein 1 and nuclear factor erythroid 2-related factor 2, or the UPS or autophagy–lysosome pathway[265–270].

Although *C. elegans* or *Drosophila melanogaster* are simple and short-lived systems, these models are useful for studying conserved mechanisms relevant to amyloidosis. Worms engineered with constitutive 20S proteasome activation display increased degradation of misfolded proteins, resistance to oxidative and heat stress, and extended lifespans at the expense of reproductive capacity[271]. Proteasome hyperactivation also rewires lipid metabolism and endoplasmic reticulum-associated degradation, suggesting broader systemic effects that could be beneficial or maladaptive depending on context. Chemical screens in nematodes have identified activators of transcription factors and chaperone programmes, including bis(phenylmethylene) cycloalkanone derivatives that activate endoplasmic reticulum membrane sensor NFE2L1 and promote proteasome biogenesis, heat-shock responses and autophagy, reducing protein aggregate burden[272]. Similarly, studies in *Drosophila* sp., in which proteostatic pathways are

Glossary

Amyloid-β precursor protein
A protein expressed by multiple cell types, including cardiomyocytes, that generates amyloid-β peptides following sequential proteolytic cleavage mediated first by β-secretase and, subsequently, by γ-secretase.

Amyloid fibrils
Insoluble, highly ordered protein aggregates characterized by a specific cross-β sheet quaternary structure; amyloid fibrils deposit in extracellular tissue spaces and disrupt organ architecture and function.

Cross-seeding
The process in which a protein monomer or aggregate acts as a 'seed', or nucleation centre, to accelerate the conversion of another protein from a soluble form to insoluble amyloid fibrils.

Free light chains
(FLCs). Immunoglobulin light chains that are not bound to heavy chains and not on amyloid fibrils. Free light chains circulate in the blood and are produced in slight excess in normal physiological conditions, but their clonal overproduction is a primary diagnostic biomarker for plasma cell dyscrasias.

Germline gene
The genetic material found in reproductive cells (germ cells) that can be passed from parents to offspring.

Immunoglobulin light chain
(IgLC). A small protein subunit that joins with a heavy chain to build an antibody. The combination of IgLC with immunoglobulin heavy chains provides the necessary diversity for the adaptive immune response to recognize foreign substances. This general term 'IgLC' does not describe whether the IgLC is bound to a heavy chain, whether it is misfolded (as an unbound, free light chain) or whether it is misfolded as part of amyloid fibrils. In IgLC amyloidosis, these amyloidogenic species can exert direct proteotoxic effects on cardiac tissue independent of macroscopic fibril deposition.

Monoclonal gammopathy
A haematological condition characterized by the abnormal, clonal proliferation of a single population of plasma cells or B cells, resulting in the secretion of a homogeneous immunoglobulin or free light chain (M-protein) into the serum or urine.

Precursor protein
A native, typically soluble physiological protein (or protein fragment) that undergoes abnormal conformational changes and misfolding to become the foundational building block of amyloid fibrils.

conserved and a pumping heart is present, show that pharmacological or genetic enhancement of proteostasis can mitigate cardiac and systemic proteotoxicity[273–276]. These models are valuable for hypothesis generation and compound prioritization but their advantages should not obscure major translational limitations, including non-human tissue architecture, compressed ageing trajectories and incomplete recapitulation of organ-specific amyloid deposition[277].

To date, most research efforts have focused on neurodegenerative models, and translating these approaches into cardiac-specific proteotoxicity assays (as in the *Drosophila* sp. model[276]) is a priority. High-throughput in vivo assays in nematodes or flies, coupled with 'heart-on-a-chip' microfluidic devices and induced pluripotent stem cell-derived cardiomyocytes, could accelerate translational potential. Ultimately, identifying and optimizing small molecules that selectively enhance proteostasis with minimal off-target effects could transform therapeutic options for cardiac and vascular proteinopathies. Overall, proteasome and autophagy modulators already under evaluation in the context of neurodegeneration might be the closest to cardiovascular translation, whereas approaches targeting tissue-specific exophers and systemic protein quality control circuits remain at an early exploratory stage. Challenges in preclinical studies aimed at identifying therapeutics for proteinopathies include the complexity and pleiotropism of these diseases, difficulties in accurately modelling human disease progression and pathology in worms and mice, and limitations relating to the assessment of early drug efficacy and end point quantification tools.

Clinical trials

Despite the benefits demonstrated with transthyretin stabilizers and *TTR* mRNA silencers (eplontersen, patisiran and vutrisiran) in ATTR, cardiovascular event rates remain high, and a proportion of patients show a limited clinical response. Therapies that actively promote the removal of existing amyloid deposits are now being explored in ongoing studies (Table 4). The monoclonal antibody NI006 that targets misfolded transthyretin is under investigation in a phase III trial[278,279]. In parallel, a phase III trial of in vivo CRISPR–Cas9 gene-editing technologies is being conducted to assess the feasibility of one-time interventions to achieve reductions in mortality and heart failure hospitalizations[280,281].

In AL amyloidosis, achieving meaningful cardiac recovery remains a key challenge. Investigative strategies aim not only to deepen the haematological response but also to reduce early mortality through faster diagnosis, improved risk stratification and optimized supportive cardiac care. Small molecules that target the IgLC dimerization interface are under development, and broader proteostasis-enhancing approaches, such as chaperone induction or autophagy modulation, remain biologically attractive[282]. Aggregation and deposited amyloid can also be targeted with monoclonal antibodies[22,24,283]. However, phase III trials involving anselamimab and birtamimab did not meet their primary end points, highlighting the difficulty of translating amyloid clearance into measurable clinical benefit[284,285]. These findings should not be overinterpreted as disproving fibril-directed therapy but they do suggest that patient selection, disease stage, end point choice, competing early mortality, and the lag between haematological control and organ recovery are crucial determinants of trial success. Effective antibody therapy might also depend on precise epitope targeting. Anselamimab acts specifically against κ-IgLC amyloid, whereas λ-directed monoclonal antibodies are also under development. However, given the potentially slow kinetics of antibody-mediated amyloid clearance, whether directly targeting amyloid deposits is the optimal strategy, or whether upstream toxic oligomers should be targeted instead remains unclear. A further unresolved question is whether truly amyloidogenic IgLCs can be identified prospectively, for example, using assays such as Amylite (Protego Biopharma). Future studies will be needed to clarify whether specific high-risk subgroups, earlier intervention or combination therapies can better capture the biological potential of these agents.

Various strategies are under early clinical investigation for Alzheimer and Parkinson diseases, including anti-α-synuclein antibodies[286], inhibition of prion-like propagation and modulation of neuroinflammation[287,288]. By stabilizing native protein folds, boosting proteostasis, inhibiting aggregation or shepherding immune clearance, these interventions create opportunities to reduce proteotoxic cardiovascular injury[283]. However, conventional randomized, controlled trial designs might not be ideal if event rates are stage-dependent, disease

subtypes are rare, and organ response lags behind haematological or biochemical changes. To address these challenges, future clinical research in PMDs will need to move beyond proof-of-concept efficacy to develop precision treatments targeting specific patient subgroups by disease stage and organ-specific time scales. To that purpose, future trials of cardiac amyloidosis should incorporate eligibility criteria such as genotype, imaging phenotype and biomarker profile, as well as baseline burden of irreversible cardiac damage. As treatment strategies evolve, trials should combine mechanistic end points with clinically meaningful outcomes and address real-world barriers related to access, tolerability and long-term monitoring.

Meta-analyses of patient-level data could potentially provide insights into the long-term effects of specific therapies. However, international, multicentre collaboration or real-world data would be essential in such analyses given that comparisons of therapies in clinical trials are unlikely. For example, in cardiac ATTR, as patients live longer with disease-modifying treatments, monitoring for emerging phenotypes and long-term safety and efficacy will become essential, underscoring the need for dynamic, adaptive research in PMDs (Box 3).

Conclusions

Cardiovascular involvement in PMDs is increasingly recognized as a major determinant of morbidity, mortality and therapeutic opportunity. Diverse misfolded proteins converge on shared pathways of proteotoxic stress, inflammation, vascular dysfunction and organ injury, underscoring the systemic nature of these disorders. Recognizing these shared molecular signatures is valuable because it enables transfer of concepts and technologies across fields. Nevertheless, this cross-fertilization should remain anchored to disease-specific biology rather than assuming interchangeability. In addition, the strength of evidence is not uniform across PMDs. Direct cardiac pathogenicity is best established for AL amyloidosis and ATTR whereas, for amyloid-β-related and α-synuclein-related cardiovascular phenotypes in humans, the literature remains more heterogeneous and often associative.

Multimodal monitoring, including advanced imaging, biomarker profiling, exercise-based functional assessment and artificial intelligence-derived tools, could facilitate the early identification of treatment responders and refine longitudinal follow-up. Combination regimens that pair amyloidogenic precursor-reducing agents with fibril-targeting therapies or cardioprotective strategies remain attractive but their promise is still largely mechanistic and requires rigorous testing across appropriately phenotyped populations.

Despite therapeutic advances, residual cardiovascular risk remains high in patients with PMDs. Addressing that risk will require a shift from late-stage symptom management towards earlier recognition of proteotoxic stress and matching of therapies to disease stage, reversibility and organ involvement. Biomarkers of vascular reactivity, proteostasis efficiency and amyloid burden could prove useful for risk stratification and treatment monitoring, but most still require prospective validation before routine adoption. Ultimately, integrating proteostasis biology into cardiovascular medicine offers a compelling framework for prevention, early detection and treatment of cardiovascular involvement in PMDs. The most robust near-term gains are likely to come from early diagnosis in established cardiac amyloidosis, whereas broader attempts to target shared proteotoxic pathways across common cardiovascular and neurodegenerative disorders remain promising but not yet clinically proven.

Published online: 05 November 2026

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Acknowledgements

K. Stamatelopoulos has received a grant on "Raising awareness and promoting timely diagnosis for TTR Amyloidosis through Digital Health" by Global Bridges/Pfizer GMG Grant project ID: 76080197, Healthcare Alliance for Amyloidosis. S.T-C. is supported by grants from the British Heart Foundation (PG/23/11093) and the Royal Society (RG\R1\241197). M.N. is supported by grants from the Telethon and CARIPLO Foundations (GJC23044), the Telethon Foundation (#5119), and the Italian Ministry of Health (Ricerca Finalizzata, grant GR-2018-12368387). T.H. is supported by the German Research Foundation Deutsche Forschungsgemeinschaft (DFG) under Germany's Excellence Strategy EXC 2030 (Project Numbers 390661388, RU 5762; 531902955, RU 2743; 388932620, SFB 1218; 269925409, SFB 1678; 520471345) and the European Research Council (ERC-AdG-101141579). N.T. is supported by a grant from the European Union Horizon Europe programme (Excellence Hubs HORIZON-WIDERA-2022-ACCESS-04-01) "CHAngeing – Connected Hubs in Ageing: Healthy Living to Protect Cerebrovascular Function", funded under grant agreement No. 101087071, and the Hellenic Foundation for Research and Innovation (grant No. HFRI—FM17C3-0869, NeuroMitophagy). K. Stellos is supported by the German Research Foundation DFG (CRC1366 C07, project no. 394046768), the German Centre for Cardiovascular Research (DZHK), and the Helmholtz Institute for Translational AngioCardioScience (HI-TAC) of the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) at Heidelberg University.

Author contributions

The authors contributed substantially to all aspects of the manuscript.

Competing interests

S.K. declares research grants to the institution from the Cantonal Hospital Baden, the Jubiläumsstiftung SwissLife, the Lindenhof Foundation, the Novartis Foundation for Medical-Biological Research, the Swiss Heart Foundation, the Swiss Society of Cardiology and the Theodor-Ida-Herzog-Egli Foundation; he has received speaker fees from the Foundation for Cardiovascular Research—Zurich Heart House and Roche Diagnostics; has received equipment and materials from Roche Diagnostics outside the submitted work; has received travel support, unrelated to this article, from the European Atherosclerosis Society, the International Atherosclerosis Society, the European Society of Cardiology, the European Society of Clinical Investigation, 4TEEN4 Pharmaceuticals, Sphingotec and PAM Theragnostics; and is a consultant to and scientific advisory board member of MDCalc. M.N. reports honoraria from Alnylam, Enodia, Janssen-Cilag and Prothena; research funding and honoraria from Pfizer; research funding and an advisory board role for Gate Bioscience; and has an advisory board role for Neurimmune. I.T. reports honoraria from Roche Diagnostics and research funding from Amgen, Onyx Pharmaceuticals and Pfizer. M.S.M. reports grant support from NIH R01HL177670 and R01AG081582; grants and personal fees from Alnylam, BridgeBio, Intellia, Ionis, Novo Nordisk and Pfizer; and personal fees from AstraZeneca and Bayer. M.F. reports consultancy for Alexion/Caelum Biosciences, Alnylam, AstraZeneca, Attralus, Bayer, Bridgbio/Eidos, Cardior, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Mycardium, Novo Nordisk, Pfizer, Prothena, and ProthenaIntellia Therapeutics and research grants from Alnylam, AstraZeneca, Bridgbio and Pfizer. K. Stellos is immediate past chair of the Professional/Public Education and Publications Committee of the Council on Genomic and Precision Medicine of the American Heart Association; he is a member of the Brain and Heart Committee of the Heart Failure Association, and ex-officio member of the Working Group on Atherosclerosis and Vascular Biology of the European Society of Cardiology; he is principal investigator of the German Center for Cardiovascular Research (DZHK) partner site Heidelberg Mannheim and adjunct principal investigator of the Helmholtz Institute for Translational Angio-Cardiac-Science (HI-TAC), and he serves as an editorial board member or associate editor for the *European Heart Journal*, *Cardiovascular Research*, *Circulation: Genomic and Precision Medicine* and *Geromedicine*. The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41569-026-01359-8.

Peer review information *Nature Reviews Cardiology* thanks Shirin Doroudgar, Olga Gursky, who co-reviewed with Shobini Jayaraman; and the other, anonymous, reviewer for their contribution to the peer review of this work.

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