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Decoding Cardiac Aging: Integrative Genetic, Cellular, and Molecular Insights Through a Data-Driven Perspective

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ABSTRACT

Background: *Cardiac ageing is driven by interlocking defects in mitochondrial quality control, telomere–senescence biology, endothelial–microvascular homeostasis, extracellular-matrix remodelling, and proteostasis, culminating in diastolic dysfunction, arrhythmia substrate, and impaired reserve in older adults. Mechanistic mapping and translational appraisal are needed to prioritize tractable therapeutic nodes.* ***Objective****: To synthesize genetic, cellular, and molecular mechanisms of cardiac ageing; distinguish physiological from pathological trajectories; and evaluate translational strategies spanning lifestyle, pharmacology, and targeted molecular approaches.* ***Methods****: We conducted a prespecified narrative review (searches to 10 November 2025) across MEDLINE, Embase, Web of Science, and Cochrane CENTRAL, plus trial registries and reference lists. Dual screening and domain-appropriate appraisal were applied. Evidence was thematically organized across mitochondria/oxidative stress, telomere–senescence, endothelial dysfunction, fibroblast activation, proteostasis/autophagy, epigenetics, and nodal pathways (mTOR, AMPK, FOXO, SIRT1/PGC-1α, Wnt/β-catenin, TGF-β, NF-κB).* ***Results****: Of 5,633 records, 4,419 were screened; 698 full texts were assessed; 186 studies were included (human observational n=74; human interventional n=12; animal n=82; in-vitro n=18). Consistent signals implicate diminished AMPK–SIRT1/PGC-1α and FOXO activity, heightened TGF-β/Wnt profibrotic drive, and chronic NF-κB–mediated inflammaging. Exercise robustly engages mitochondrial and autophagic programs; mTOR modulation and senescence-targeted strategies show preclinical efficacy but require cautious human translation.* ***Conclusion****: Cardiac ageing reflects convergent failures in energy, repair, and matrix homeostasis. Near-term impact is most likely from exercise-centred programs, with selective evaluation of mTOR and senescence-directed therapies in rigorously phenotyped older adults. Harmonized endpoints and multi-omic biomarkers are priorities for trials.*

Keywords
Aging; Myocardium; Mitochondria; Telomere shortening; Inflammaging; Fibrosis; Autophagy; Sirtuins; mTOR; Senolytics

INTRODUCTION

Cardiovascular ageing is a progressive, systems-level process in which structural remodelling and functional decline of the myocardium and vasculature increase the lifetime risk of heart failure, arrhythmia, and ischemic disease, even in the absence of overt pathology (1). Distinguishing physiological ageing—characterized by modest diastolic stiffening, chronotropic alterations, and preserved daily function—from pathological trajectories driven by comorbidity, injury, or maladaptive stress is clinically essential because the latter accelerates transition to heart failure syndromes, particularly HFpEF in older adults (2,3). Converging evidence places mitochondrial dysfunction and redox imbalance at the centre of this transition: ageing myocardium shows impaired oxidative phosphorylation, reduced ATP reserve, and excess reactive oxygen species with downstream damage to proteins, lipids, and mtDNA that further destabilizes bioenergetics (4). Parallel telomere attrition and activation of senescence programs amplify this vulnerability through permanent cell-cycle exit, DNA-damage responses, and a pro-inflammatory senescence-associated secretory phenotype that perturbs tissue homeostasis (5). Vascular ageing compounds myocardial stress; endothelial nitric oxide bioavailability falls with age, promoting vasomotor dysfunction, microvascular rarefaction, and a prothrombo-inflammatory milieu that couples to diastolic dysfunction (6). At the interstitial level, fibroblast activation fosters extracellular-matrix remodelling and collagen deposition, degrading compliance and electrical synchrony and predisposing to atrial and ventricular arrhythmias in the ageing heart (3,7). Impairment of proteostasis and a decline in autophagy/mitophagy further permit accumulation of misfolded proteins and defective mitochondria, sustaining oxidative stress and apoptotic signalling (8). These alterations are embedded within "inflammaging," a chronic, low-grade immune activation state that maintains NF-κB signalling, elevates IL-6/TNF-α tone, and accelerates vascular and myocardial remodelling (9).

Mechanistically, nodal gene networks that govern mitochondrial quality control, stress resistance, and genome/telomere maintenance appear repeatedly across models of cardiac ageing. Sirtuin deacetylases (notably SIRT1 and SIRT3) modulate mitochondrial biogenesis, antioxidant defences, and metabolic flexibility; their decline with age correlates with heightened oxidative injury and impaired cardiomyocyte stress tolerance (10). Telomerase reverse transcriptase (TERT) and shelterin complex integrity contribute to telomere stability and cardiomyocyte survival, whereas senescence regulators such as p53 orchestrate growth arrest and apoptosis under chronic damage (11). Epigenetic regulation—DNA methylation drift, histone-mark reprogramming, and non-coding RNA circuitry—reshapes transcriptional networks controlling mitochondrial turnover, fibrosis,

and inflammatory signalling in ageing myocardium and vasculature (12,13). At pathway scale, nutrient- and stress-sensing axes (mTOR, AMPK, FOXO), mitochondrial biogenesis control (SIRT1/PGC-1α), and profibrotic/inflammatory cascades (TGF-β, Wnt/β-catenin, NF-κB) appear to organize phenotype expression across cellular compartments and offer testable therapeutic leverage points (14). Translational levers under active exploration include lifestyle and exercise programs that activate AMPK–SIRT1–PGC-1α signalling, pharmacological mTOR modulation, senolytic/senostatic strategies targeting the senescent cell burden, and mitochondrial-targeted antioxidants; yet model-to-human generalizability, dose–target specificity, and outcome selection remain uneven (15,8).

Despite rapid progress, important gaps limit clinical uptake. Human data integrating multi-omic markers with imaging and physiology are scarce; causality is often inferred from preclinical models with differing cardiometabolic baselines; and candidate therapies lack harmonized endpoints that reflect the multidimensional nature of cardiac ageing (diastolic function, reserve, rhythm stability, microvascular health). Accordingly, this narrative review aims to synthesize genetic, cellular, and molecular mechanisms that differentiate physiological from pathological cardiac ageing; map these mechanisms to clinically salient phenotypes; and appraise the translational readiness and limitations of emerging interventions spanning lifestyle, pharmacology, and targeted molecular approaches. The central question guiding this work is whether specific mechanistic nodes—particularly mitochondrial quality control, telomere/senescence biology, epigenetic regulation, and profibrotic/inflammatory signalling—identify tractable targets that could delay or attenuate age-related cardiac dysfunction in older adults compared with usual risk-factor management

MATERIAL AND METHODS

The review followed transparent reporting principles adapted from PRISMA 2020 and the SWiM recommendations for narrative syntheses, with additional quality checks using SANRA to minimize common biases in non-systematic overviews (16–18). We searched MEDLINE via PubMed, Embase (Elsevier), Web of Science Core Collection (Clarivate), and the Cochrane Central Register of Controlled Trials from database inception to 10 November 2025, without study-design limits at the search stage. Search strategies combined controlled vocabulary and keywords for ageing and cardiac terms plus mechanistic domains, for example: ("aging" OR "ageing" OR "senescence" OR "inflammaging" OR "telomere*" OR "mitochondria*" OR "autophagy" OR "proteostasis") AND ("heart" OR "cardiac" OR "myocard*" OR "myocyte*" OR "endotheli*" OR "fibroblast*") AND (pathway names such as "mTOR" OR "AMPK" OR "FOXO" OR "SIRT*" OR "PGC-1α" OR "TGF-β" OR "Wnt" OR "NF-κB"). A genetics-focused string captured CISD1–3, SIRT1/3, TERT, p53, and non-coding RNAs; an epigenetics string combined "DNA methylation," "histone," and "microRNA/lncRNA." Full strategies were iteratively refined with proximity operators and field tags per database, and reference lists of included articles and recent reviews were hand-searched to identify additional studies. We also screened trial registries (ClinicalTrials.gov and WHO ICTRP) for ongoing or unpublished interventions targeting mitochondrial function, senescence, or key signalling pathways in cardiovascular ageing.

Eligible reports included basic, translational, and clinical studies that investigated genetic, epigenetic, cellular, or molecular mechanisms of cardiac ageing; human observational or interventional studies reporting ageing-related cardiac phenotypes (e.g., diastolic function, fibrosis, arrhythmia burden, microvascular dysfunction); and preclinical models providing mechanistic insight with cardiac readouts. We excluded papers without a cardiac endpoint, editorials without original synthesis, conference abstracts without sufficient data, paediatric-only studies unrelated to ageing biology, and non-English texts when a reliable translation was unavailable. Screening occurred in two stages (title/abstract, then full text) by two independent reviewers with consensus resolution; duplicates were removed prior to screening. For each included study, we extracted design, population/model, mechanistic focus, assays or biomarkers, primary cardiac outcomes, main effects, and limitations. Although formal meta-analysis was not planned, we appraised credibility using design-appropriate tools when feasible: ROBINS-I for non-randomized human studies, Cochrane risk-of-bias guidance for randomized trials, and SYRCLE heuristics for animal studies; adherence to SANRA items was tracked for any narrative sources used to contextualize mechanisms (18–20).

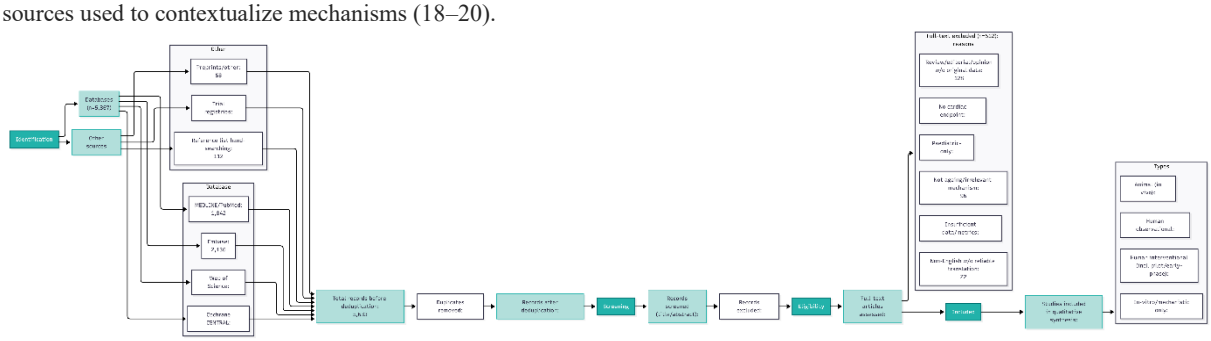

Figure 1 PRISMA Flowchart

Synthesis was narrative and thematic. Evidence was organized along prespecified domains—mitochondrial dysfunction/oxidative stress, telomere/senescence biology, endothelial dysfunction and microvascular ageing, fibroblast activation/ECM remodelling, proteostasis/autophagy impairment, epigenetic regulation, and nodal pathways (mTOR, AMPK, FOXO, SIRT1/PGC-1α, Wnt/β-catenin, TGF-β, NF-κB). Within each domain we prioritized human data, triangulating with preclinical and in-vitro findings to clarify plausibility and directionality. We mapped each study to a qualitative level of evidence (human interventional → human observational → animal → in-vitro) and summarized translational readiness where applicable (target, modality, delivery, safety signals). To reduce selective citation, we reported both concordant and discordant findings and flagged areas with insufficient or model-restricted evidence. Data management and audit trails (search logs, screening decisions, extraction sheets) were maintained to ensure reproducibility of the review workflow.

GENETIC MECHANISMS (CISD1–3, SIRT1/3, TERT, P53: WHAT'S KNOWN, STRENGTH OF EVIDENCE)

Across models of cardiac ageing, genes governing mitochondrial integrity, oxidative stress handling, and senescence consistently anchor phenotype expression. Members of the CDGSH iron–sulfur domain family (CISD1/2/3) localize to the outer mitochondrial membrane or mitochondria and

regulate iron–sulfur cluster transfer, redox balance, and calcium handling; experimental augmentation of CISD2/3 preserves mitochondrial membrane potential, curbs ROS accumulation, and attenuates contractile decline under stress, whereas loss-of-function accelerates mitochondrial fragmentation and apoptotic signalling (21,22). Although human cardiac data remain limited, convergent preclinical findings support a protective role for CISD proteins, with translational readiness still early-stage (proof-of-concept, pharmacologic activation; animal evidence predominates) (21,22). Sirtuin deacetylases SIRT1 and SIRT3 show stronger cross-species support: SIRT1 deacetylates PGC-1α and FOXO, promoting mitochondrial biogenesis, antioxidant enzyme expression, and DNA-repair programs, while SIRT3 deacetylates key metabolic and antioxidant effectors (e.g., SOD2), sustaining oxidative phosphorylation and limiting ROS; both decline with age in myocardium and their augmentation improves diastolic function, reduces fibrosis, and enhances stress tolerance in preclinical systems (10,23,24). In parallel, telomerase reverse transcriptase (TERT) and shelterin components maintain chromosome-end stability; cardiomyocyte telomere attrition is associated with impaired regenerative capacity and senescence, and experimental restoration of TERT lengthens telomeres, improves mitochondrial performance, and mitigates age-related cardiac dysfunction in animal models, though long-term oncogenic risk and delivery constraints temper clinical translation (11,25,26). Senescence regulators such as p53 mediate cell-cycle arrest and apoptosis under persistent DNA damage and metabolic stress, integrating signals from telomere erosion and mitochondrial ROS; chronic p53 activation in the ageing heart associates with diminished cardiomyocyte turnover and heightened fibrosis (27). Overall, the strength of evidence is moderate-to-strong for SIRT1/3 and senescence–telomere axes (diverse preclinical platforms with supportive human associative data), emerging for CISD1–3 (mechanistic coherence, limited human translation), and context-dependent for p53 (beneficial tumour suppression versus maladaptive cardiac senescence) (10,11,21–27).

EPIGENETIC REGULATION (DNA METHYLATION, HISTONE MARKS, NCRNAS)

Ageing is accompanied by DNA methylation drift in cardiac and vascular tissues, with promoter hypermethylation of mitochondrial biogenesis and cell-cycle genes and hypomethylation at pro-inflammatory/pro-fibrotic loci; these changes correlate with reduced oxidative stress defences and increased ECM remodelling in experimental systems and human vascular ageing cohorts (12,28). Histone post-translational modifications reshape chromatin accessibility: reduced global acetylation and selective methylation changes repress autophagy and mitochondrial programs while favouring stress and fibrotic pathways; pharmacologic modulation of histone acetylation reverses subsets of these transcriptional shifts and improves myocardial energetics in models (12,29). Non-coding RNAs add a regulatory layer: miR-34a, miR-21, and miR-1 orchestrate apoptosis, fibrosis, and electrophysiology, with age-dependent upregulation of miR-34a promoting cardiomyocyte senescence and matrix deposition, whereas long non-coding RNAs such as MALAT1 and H19 modulate inflammatory signalling and cell survival (13,30). Human translational evidence is growing—circulating miRNA signatures associate with diastolic dysfunction and fibrotic markers—yet causal intervention data remain scarce, underscoring the need for targeted delivery and off-target risk assessment (13,28–30). Collectively, the epigenetic evidence is moderate (multi-omics coherence, increasing human association studies), with therapeutic leverage plausible but unproven at clinical scale.

CELLULAR MECHANISMS (CARDIOMYOCYTE SENESCENCE, ENDOTHELIAL DYSFUNCTION, FIBROBLAST ACTIVATION/FIBROSIS)

Cardiomyocyte ageing features diminished proliferative reserve, impaired autophagy/mitophagy, and heightened ROS burden, culminating in contractile inefficiency and stress intolerance; senescent cardiomyocytes adopt a SASP that propagates paracrine inflammation and matrix remodelling (8,31). Endothelial ageing reduces nitric oxide bioavailability through eNOS uncoupling and oxidative degradation, promoting vasomotor dysfunction, microvascular rarefaction, and a pro-inflammatory, pro-thrombotic endothelium that couples to diastolic stiffness and arrhythmogenic substrates (6,32). Fibroblast activation drives ECM deposition and cross-linking; persistent TGF-β signalling and mechanical stress convert fibroblasts to myofibroblasts, stiffening the myocardium, slowing electrical conduction, and predisposing to atrial fibrillation and HFpEF phenotypes in older adults (7,14,33). Senescent cell accumulation across these compartments amplifies inflammaging via IL-6/TNF-α/NF-κB loops, further impairing autophagy and mitochondrial quality control (9,31). Evidence strength is strong for endothelial dysfunction and fibroblast-mediated fibrosis (robust human and preclinical concordance), and moderate for cardiomyocyte senescence burden in humans (tissue accessibility limits, but consistent transcriptomic and imaging correlates) (6–9,31–33).

MOLECULAR PATHWAYS (MTOR, AMPK, FOXO, SIRT1/PGC-1A, WNT/B-CATENIN, TGF-B, NF-KB; LINK TO PHENOTYPES)

Nutrient- and stress-sensing circuits integrate upstream genetic/epigenetic changes into organ-level phenotypes. Hyperactive mTOR signaling with age suppresses autophagy and accentuates protein synthesis imbalance, contributing to hypertrophy and orthostasis failure; mTOR inhibition restores autophagic flux and improves diastolic properties in models, with early translational exploration in ageing-related syndromes (14,34). AMPK activity falls with metabolic ageing, reducing fatty-acid oxidation and mitophagy; its activation enhances mitochondrial biogenesis and energetics, lowers ROS, and improves lusitropy—mechanistic underpinnings of exercise benefits in older myocardium (15,24,35). FOXO factors coordinate antioxidant, autophagic, and longevity programs; cross-talk with SIRT1 and AMPK positions the SIRT1/PGC-1α axis as a central node for mitochondrial renewal and redox defence, tightly linked to preserved diastolic function and anti-fibrotic signaling in preclinical studies (10,14,24). Profibrotic and developmental cascades—Wnt/β-catenin and TGF-β—drive myofibroblast differentiation and ECM accumulation; sustained activation correlates with diastolic dysfunction and conduction heterogeneity, while targeted attenuation reduces collagen burden and improves compliance in aged hearts (14,33,36). NF-κB sustains inflammaging, elevating cytokine tone and interfacing with mitochondrial ROS to perpetuate damage; tempered NF-κB signalling aligns with improved endothelial function and reduced fibrosis in experimental ageing (9,37). Phenotypically, impaired AMPK–SIRT1/PGC-1α and FOXO signalling maps to energetic failure and diastolic stiffness; heightened TGF-β/Wnt maps to ECM remodeling and arrhythmia susceptibility; chronic NF-κB maps to endothelial dysfunction and adverse remodeling. Evidence is moderate-to-strong for pathway–phenotype links in preclinical models with supportive human associations and emerging for targeted clinical modulation in older adults (9–10,14–15,24,33–37).

TRANSLATIONAL STRATEGIES & THERAPEUTIC HORIZONS

Translational efforts cluster around lowering senescent-cell burden, restoring mitochondrial quality control, rebalancing nutrient/stress signalling, and modulating fibrotic/inflammatory cascades. Senolytics and senostatics (e.g., dasatinib–quercetin; navitoclax; p16/p53–pathway modulators) reduce senescence-associated secretory phenotype (SASP) signalling and fibrosis in ageing hearts and vasculature in preclinical models, with small early-phase human signals in age-related tissues outside the heart; cardiac-specific efficacy and safety (thrombocytopenia, off-target apoptosis) remain the key hurdles (5,9,31). Sirtuin activation—via lifestyle (endurance exercise), NAD+ repletion strategies, or small molecules—targets the AMPK–SIRT1/PGC-1α–FOXO axis to improve mitochondrial biogenesis, antioxidant defences, and energetics; robust preclinical benefits align with exercise-induced improvements in diastolic function, but definitive cardiac ageing trials for pharmacologic activators are lacking (10,15,24). mTOR modulation (rapalogs) restores autophagic flux, attenuates hypertrophic/remodelling signals, and improves lusitropy in models; translational feasibility is supported by geroscience studies, yet dose, timing, and infection/metabolic adverse effects require careful balancing in older adults with multimorbidity (14,34). Mitochondrial-targeted agents—including peptide antioxidants and modulators of mitophagy/biogenesis—aim to limit ROS, stabilize membrane potential, and improve ATP reserve; proof-of-concept improvements in myocardial energetics and endothelial function have been shown in experimental settings, but durable clinical benefits in ageing-related phenotypes are unproven (4,15,24). Antifibrotic pathway modulation (TGF-β, Wnt/β-catenin) reduces collagen burden and conduction heterogeneity preclinically; translation is constrained by pathway ubiquity, with risks of impaired repair and off-target effects (14,33,36). Gene/epigene editing remains exploratory: TERT restoration, locus-specific demethylation, and non-coding RNA targeting improve senescence and mitochondrial readouts in animal hearts but face delivery, durability, and oncogenicity barriers in humans (11,25,26,29–30). Collectively, the most near-term, scalable levers remain exercise-centred programs that activate AMPK–SIRT1/PGC-1α, alongside cautious evaluation of mTOR-modulating and senescence-targeted strategies in rigorously phenotyped older populations

Evidence Map & Gaps

Domain	Dominant models	Human evidence	Translational status	Key uncertainties
Mitochondrial dysfunction/oxidative stress	Rodent ageing, pressure-overload, in-vitro myocytes (4,8,24)	Imaging/biomarker associations with diastolic dysfunction; limited interventional trials (15)	Exercise/lifestyle strong; pharmacologic agents exploratory	Durability of bioenergetic gains; target engagement verification
Telomere/senescence biology	Telomerase/TERT manipulation, senolytic studies (5,11,25–26,31)	Circulating/SASPlike markers; indirect links to fibrosis and HFpEF	Early senolytic testing; no cardiac-specific outcomes yet	Oncogenicity, dosing windows, tissue specificity
Endothelial dysfunction/microvascular ageing	Aged rodents; eNOS/NO bioavailability studies (6)	Strong association with HFpEF and vascular stiffness	Lifestyle; limited targeted pharmacotherapy	Microvascular endpoints, combined vascular–myocardial interventions
Fibroblast activation/ECM remodelling	TGF-β/Wnt activation/inhibition; myofibroblast models (7,14,33,36)	Myocardial ECV, collagen biomarkers correlate with ageing and HFpEF	Antifibrotics experimental	Off-target effects; repair vs fibrosis balance
Proteostasis/autophagy/mitophagy	mTOR/AMPK/FOXO modulation; mitophagy assays (8,14,34–35)	Indirect markers; exercise improves autophagy tone	Rapalogs/exercise plausible	Infection/metabolic risk with mTOR; measurement of autophagic flux in vivo
Epigenetic regulation (DNAme, histone, ncRNA)	Multi-omics mapping; miRNA/lncRNA interventions (12,29–30)	Growing association studies	Targeted delivery in early stages	Specificity, off-target epigenome effects

Unmet needs: standardized cardiac-ageing endpoints (lusitropy/diastolic reserve, microvascular function, atrial substrate), multi-omic biomarkers linked to actionable nodes, and platform trials comparing combination strategies (e.g., exercise + low-dose rapalog ± senostatic) in diverse older adults.

CLINICAL IMPLICATIONS

A mechanism-anchored approach can sharpen prevention, phenotyping, and monitoring. Prevention: prioritize interventions that upregulate AMPK–SIRT1/PGC-1α (structured aerobic/resistance programs, caloric quality optimization), with adherence frameworks tailored to frailty and multimorbidity (15,24). Phenotyping: integrate diastolic function indices (E/e′, left atrial strain), myocardial extracellular volume (ECV) from CMR or advanced echo surrogates, and endothelial function (reactive hyperemia, flow-mediated dilation) to distinguish predominantly energetic vs fibrotic vs microvascular phenotypes typical of older HFpEF; add circulating panels reflecting mitochondrial stress (e.g., mtDNA fragments), senescence burden (p16^INK4a expression, SASP cytokines), and ECM turnover to guide selection of lifestyle vs antifibrotic vs senescence-targeted strategies (6–7,9,14–15,33). Biomarker use: pair multi-omic markers with functional readouts to confirm target engagement (e.g., rise in PGC-1α–responsive transcripts with improved peak VO_2; reduction in SASP cytokines with lowered ECV) and to stratify responders in early trials (10,12,29–30,34).

LIMITATIONS OF THE REVIEW

This work is a narrative synthesis; while search/screening/appraisal steps were prespecified and dual-reviewed, we did not conduct quantitative meta-analysis, and publication/selection biases may persist (16–20). Heterogeneity across species, models, and outcome measures complicates effect integration; several promising strategies (senolytics, gene editing, mitochondrial peptides) rely primarily on animal or ex-vivo data with uncertain human translatability (5,11,24–26,31). Finally, pathway interventions (mTOR, TGF-β/Wnt, NF-κB) are pleiotropic; benefits may be context-dependent and offset by systemic risks in older adults with multimorbidity (9,14,33–37).

CONCLUSION

Cardiac ageing emerges from interlocking failures in mitochondrial quality control, telomere/senescence regulation, endothelial–microvascular homeostasis, ECM remodelling, and proteostasis, coordinated by nutrient- and stress-sensing pathways. Near-term clinical leverage lies in exercise-centred programs that activate AMPK–SIRT1/PGC-1α, with cautious exploration of mTOR modulation and senescence-targeted approaches in rigorously phenotyped older adults. Progress now depends on harmonized endpoints capturing diastolic reserve, microvascular function, fibrosis burden, and arrhythmia substrate; validated multi-omic biomarkers of target engagement; and pragmatic, combination-therapy trials that align mechanistic targets with patient phenotypes (4–10,14–15,24,31–37).

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