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REVIEW

Anti-senescence therapies: a new concept to address cardiovascular disease

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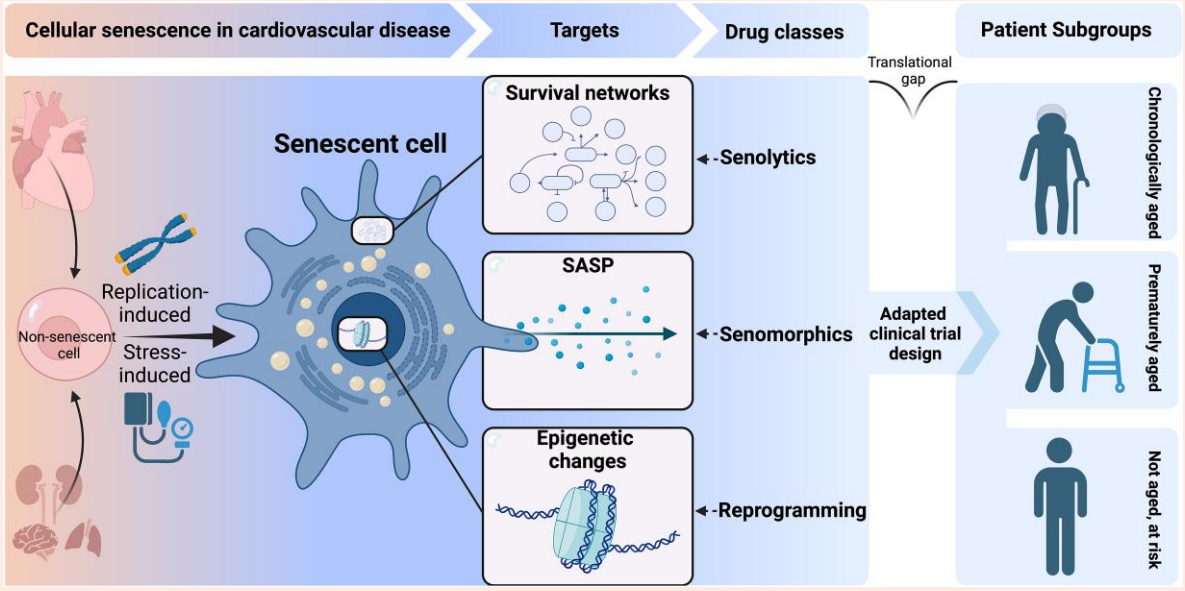
Abstract

Accumulation of senescent cells is an increasingly recognized factor in the development and progression of cardiovascular (CV) disease (CVD). Senescent cells of different types display a pro-inflammatory and matrix remodelling molecular programme, known as the 'senescence-associated secretory phenotype' (SASP), which has roots in (epi)genetic changes. Multiple therapeutic options (senolytics, anti-SASP senomorphics, and epigenetic reprogramming) that delete or ameliorate cellular senescence have recently emerged. Some drugs routinely used in the clinics also have anti-senescence effects. However, multiple challenges hinder the application of novel anti-senescence therapeutics in the clinical setting. Understanding the biology of cellular senescence, advantages and pitfalls of anti-senescence treatments, and patients who can profit from these interventions is necessary to introduce this novel therapeutic modality into the clinics. We provide a guide through the molecular machinery of senescent cells, systematize anti-senescence treatments, and propose a pathway towards senescence-adapted clinical trial design to aid future efforts.

Graphical Abstract



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Towards anti-senescence therapeutic in cardiovascular (CV) disease. Non-senescent cells in the CV system, but also other organs, enter senescence via replicative exhaustion or molecular stress. Senescent cells show key targetable features, survival networks, the senescence-associated secretory phenotype (SASP), and epigenetic changes, and these can be modulated via the three anti-senescence drug classes: senolytics, senomorphics (anti-SASP), and reprogramming. Senescence-adapted clinical trial design is necessary to bring these therapeutics to distinct patient subgroups. Created in BioRender.com.

Keywords Senescence • Ageing • Cardiovascular • Therapies • Clinical trials

1. Introduction to cellular ageing—unmet needs and novel therapeutic targets

Ageing is the strongest risk factor associated with cardiovascular (CV) disease (CVD) and is integrated in various CV risk scoring systems (PROCAM, ESC, Reynolds, Framingham, and Diamond Forrester).[1] Ageing is traditionally considered an unmodifiable CVD risk factor. However, the ageing process is more than a passive timeline that aggregates long-term effects of classical risk factors such as arterial hypertension, hyperlipidaemia, diabetes mellitus, obesity, and smoking.[2] A large portion of CV risk with ageing is unexplained by longer exposure to classical risk factors.[2,3] Traditional CVD factors play a decreasing contribution to overall risk in later years of life.[4] Despite increases in average life spans in the western world, improvements in health span are lagging behind.[5,6] The overall expanding ageing population is thus left with limited options to improve health and quality of life.[7,8] Additionally, the process of ageing does not exclusively correlate with chronological age, as various chronic stressors including classical CV risk factors may trigger ageing processes prematurely, leading to CVD, increased biological age, and ultimately worsened clinical outcomes.[1,9]

Ageing is an active and biologically regulated process on a cellular level. Cellular senescence is the fundamental basis of ageing. Senescent cells accumulate in different organs and drive chronic diseases such as heart failure,[10–14] atherosclerosis,[1,15] arterial hypertension,[16,17], atrial fibrillation,[18] diabetes,[19] renal failure,[20] liver steatosis,[21,22] osteoporosis,[23] cancer,[24] lung fibrosis,[25,26] chronic obstructive pulmonary disease,[27] Alzheimer's disease,[28] and other.

Cellular senescence is defined as persistent cell cycle arrest.[29,30] The senescence programme activated in different cell types due to either replicative exhaustion (telomere shortening–induced senescence) or stress (DNA damage–induced senescence, mitochondrial dysfunction–induced senescence, and perturbed proteostasis).[30] Although senescent cells have initial physiological roles in embryonic development, tissue repair, and tumour supression,[24,31–33] re-occurring or non-resolved damage leads to an increased load of senescence in various organs.[34] These cell populations resist cell death and immune clearance in pathological conditions and act as a persisting driver of chronic disease, even in smaller cell numbers.[1] Furthermore, immune cells undergo senescence, further exacerbating chronic organ deterioration.[35] Both telomere-induced and stress-induced senescence act in concordance to promote the ageing processes.[1]

Since ageing is in part inevitable, an immense challenge exists to develop therapeutics and identify populations of patients who likely to profit from anti-senescence interventions. Current designs of clinical trials may be insufficient to test clinical effects of agents targeting senescence.

In this review, we provide an overview of molecular entry points for anti-senescence therapeutics and analyse advantages and drawbacks of different strategies depending on the clinical context of CVD. Furthermore, we propose a strategy to allow optimal patient group selection and identify knowledge gaps that need resolution to bring therapies targeting cellular senescence to appropriate patient populations.

2. The molecular machinery of senescence

Proliferation blockade is a central feature of cellular senescence, occurring predominantly at the G1/S checkpoint through two main pathways. The first centred around p53/p21$^{WAF1/CIP1}$, which suppress cyclin-dependent kinase (CDK) 2 and cyclin E2 as a part of the DNA damage response.[36] Sub-lethal, persistent, und unresolved DNA damage causes p53 nuclear translocation with subsequent p21 activity.[37] The second main pathway suppresses CDK4/6 via the tumour suppressor p16. This pathway utilizes DNA-independent sensing on an epigenetic level.[38] Both pathways act in concordance to suppress the phosphorylation of the retinoblastoma protein (Rb) protein, ultimately arresting proliferation.[36] The mentioned cell cycle inhibitors display a dynamic expression pattern. p53/p21$^{WAF1/CIP1}$ is activated early in senescence cell cycle arrest, while p16 persists in the long term.[15] Furthermore, expression patterns differ between cell types and tissues.[39,40]

Aberrations in cellular senescence extend beyond proliferation arrest, as these cells display significant activity by secreting a plethora of factors named the senescence-associated secretory phenotype (SASP). SASP contains multiple pro-inflammatory [interleukin (IL) IL-1α, IL-1β, IL-6, IL-8, IL-18, high-mobility group protein B1 (HMGB-1), macrophage inflammatory protein (MIP)-1a, MIP-3a, granulocyte-macrophage colony-stimulating factor, and tumour necrosis factor (TNF)-α],[1,15,41,42] extracellular matrix remodelling [matrix metalloproteinase (MMP)-1, -2, -3, -7, -8, -9, -10, -12, -13, and -14][1,43–46] and coagulation-modulating factors (tissue factor pathway inhibitor, calumenin, plasminogen activator inhibitor 1 (PAI-1), PAI-2, SERPINE 2, and SERPINE B6).[47] Furthermore, the SASP induces a paracrine environment that propagates senescence to neighbouring cells.[48] The list of SASP factors mentioned here is not exhaustive. The SASP is variable and depends on senescence-inducing stimulus, cell type, and temporal dynamics, as previously reviewed.[1]

Another feature of senescence is the resistance towards cell death. Senescent cells depend on molecular pro-survival networks.[49] B-cell lymphoma (BCL)-2, BCL-W, and BCL-XL in senescent cells hamper the intrinsic apoptotic pathway.[50] Furthermore, senescent cells up-regulate mammalian target of rapamycin (mTOR) and p38 mitogen-activated protein kinases (p38-MAPK) as significant survival pathways.[49] They also delay death via the oxidation resistance 1 protein,[51] as well as insulin-like growth factor 1 receptor-phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt)[52] and yes-associated protein-TEA/ATSS domain transcription factor (TEAD) pathways.[53]

Senescent cells also evade death through resistance to scavenging and removal by immune cells. Senescent cells are physiologically removed by natural killer (NK) and T cells in settings of embryonic development or after acute tissue injury via the granzyme-perforin system.[54,55] In pathological conditions, senescent cells exert complex paracrine effects that inhibited T-cell memory[56] and effector responses,[57] as well as macrophage scavenging.[58] Senescent cells also evade clearance by the immune system by overexpressing functionless decoy receptors (DCR)-1 (TNF receptor superfamily member 10C) and DCR-2 (TNF receptor superfamily member 10D), thus disabling TNF-related apoptosis—inducing ligand extrinsic apoptotic signalling.[54] The up-regulation of DCR-1 is a consistent feature of otherwise heterogenous senescent cells.[40] Senescent cells also escape

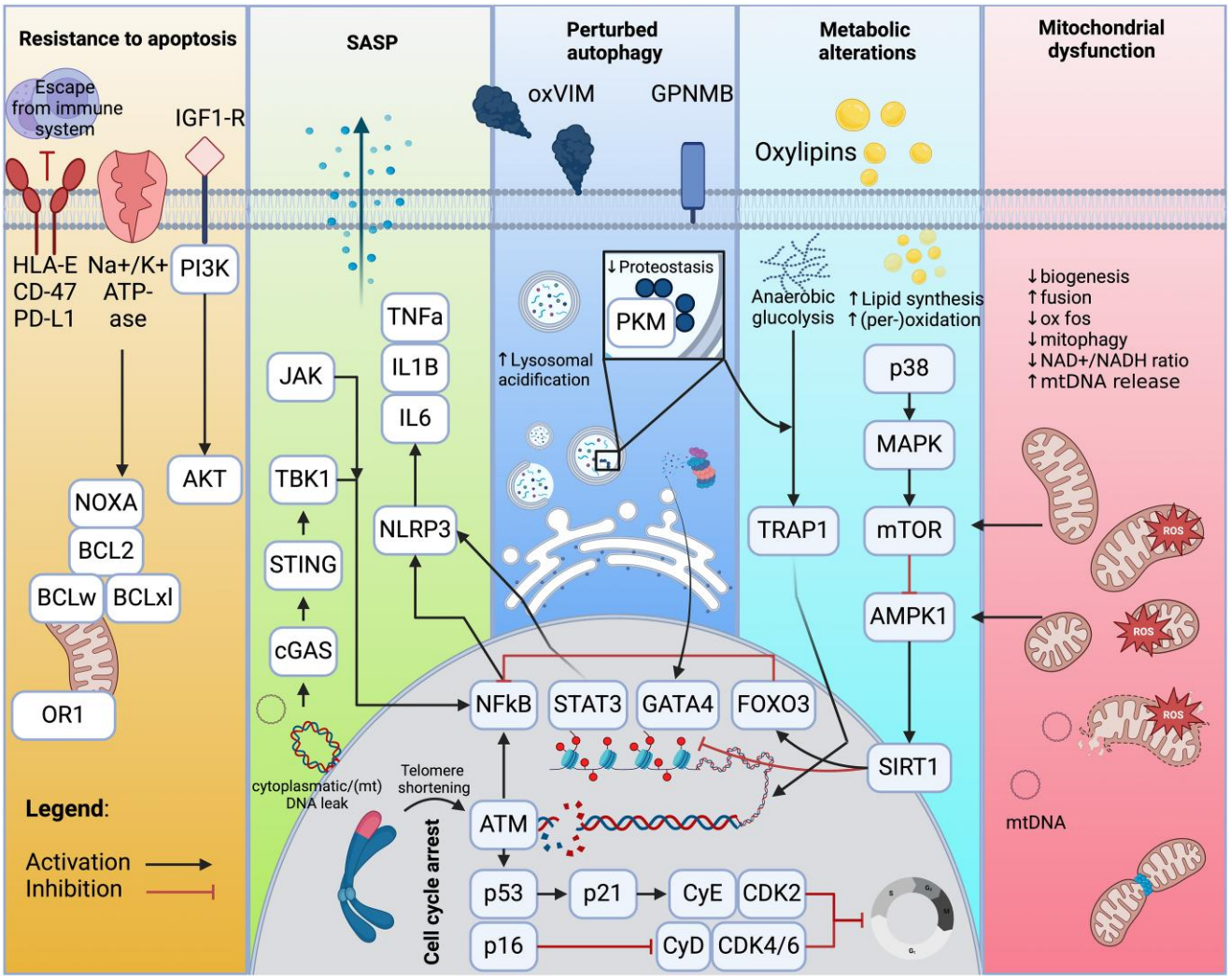

Figure 1 Core features of cellular senescence: resistance to apoptosis, SASP, perturbed autophagy and proteostasis, metabolic alterations, and mitochondrial dysfunction. AKT, Akt kinase; ATM, ATM serine/threonine kinase; BCL, B-cell lyphoma; CD47, cluster of differentiation 47; CyD/E, cyclin D/E; cGAS, cyclic GMP-AMP synthase; CDK, cyclin-dependent kinase; FOXO3, forkhead box O3; GATA4, GATA binding protein 4; HLA-E, HLA Class I histocompatibility antigen E, alpha chain E; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; mtDNA, mitochondrial DNA; Na+/K+, ATPase sodium–potassium pump; NAD, nicotinamide adenine dinucleotide; NLRP3, NLR family pyrin domain containing 3; NOXA, protein Noxa; OR1, oxidation resistance 1; oxVIM, oxidized vimentin; ox fos, oxidative phosphorylation; p21, cyclin-dependent kinase inhibitor 1; PKM, pyruvate kinase; p38-MAPK, p38 mitogen-activated protein kinases; p53, cellular tumour antigen p53; SIRT1, sirtuin 1; STING, stimulator of interferon genes; STAT3, signal transducer and activator of transcription 3; TBK1, TANK-binding kinase 1; TRAP1, TNF receptor associated protein 1. Created in BioRender.com.

elimination via NK and T cells by up-regulating human leucocyte antigen (HLA)-E[59] and the programmed death-ligand 1 (PD-L1).[60]

Immune cells themselves undergo senescence and contribute to the feed-forward loop of chronic inflammation. Several T-cell clusters carry features of senescence (CD-28 and CD-27 negative; high expression of Tim-3, CD-57, killer cell lectin-like receptor subfamily G member 1, and CD-45).[35,61] Senescent T cells, such as CD-4–positive and CD-45 re-expressing cells, also described as CD-4+ terminal effector memory T cells (T-EMRA), display a SASP with multiple pro-inflammatory cytokines (C-X-C chemokine receptor 3, TNF-α, interferon gamma, and others).[35,62–64] These cells also showed anti-apoptotic features by up-regulating BCL-2 and unusual toxic activity towards atherosclerotic plaque endothelium,[64] possibly destabilizing atherosclerotic plaques and triggering acute myocardial infarction.[1] Senescent cytotoxic CD-8+ T cells show decreased antigen-specific activity and increased unspecific killing.[61] Macrophages expressing senescence markers promoted atherosclerosis.[65]

The molecule in inter-play between key features of senescence is complex. It represents an intertwined network between reactive oxygen species (ROS), DNA damage repair, hampered autophagy, mitochondrial dysfunction, epigenetic pathology, and various stress pathways. These processes are summarized in *Figure 1*.

3. Classification and general features of anti-senescence therapeutics

Several therapeutic strategies have been developed to address these various factettes of senescence.

Anti-senescence therapeutics are divided into senolytics, senomorphics (anti-SASP), and reprogramming approaches.

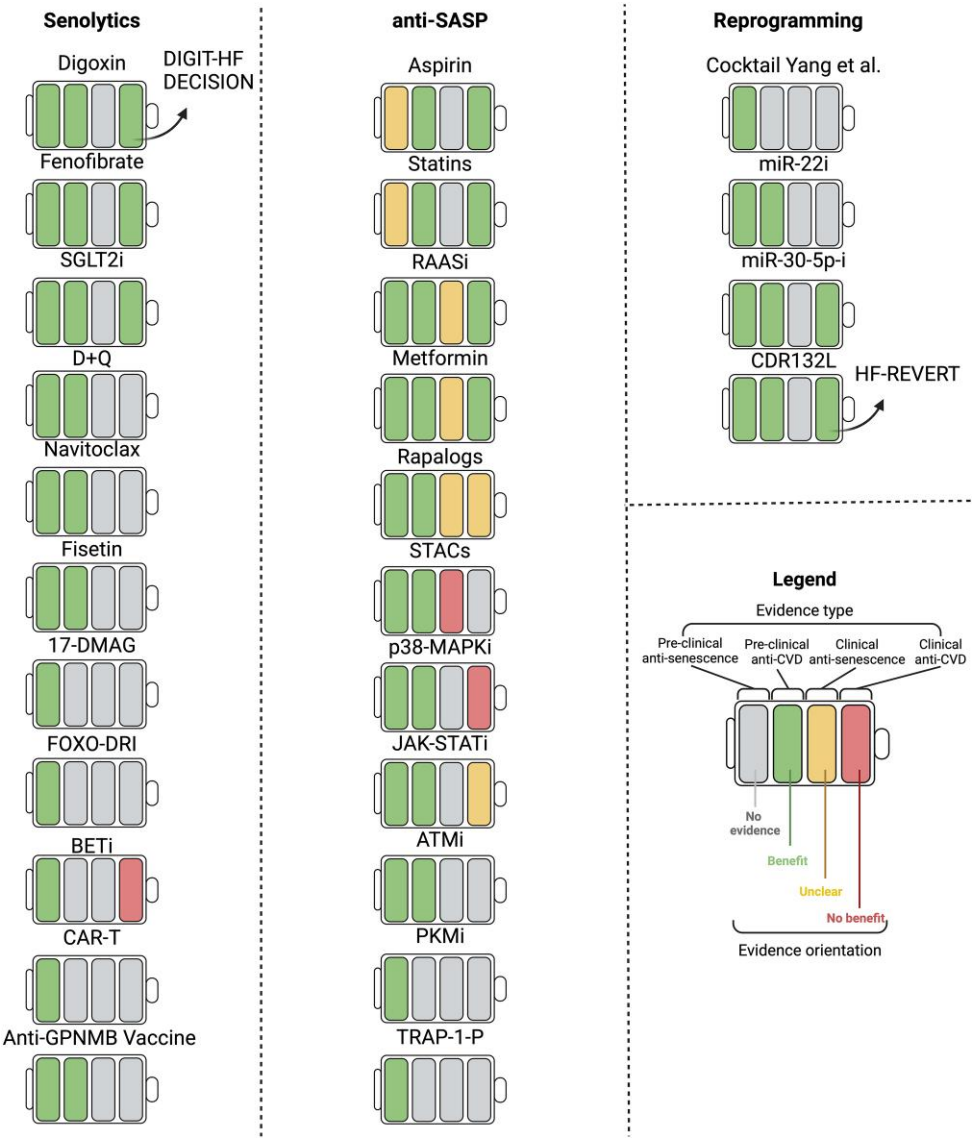

Figure 2 Classification and overview of evidence grade for anti-senescence therapeutics. ATMi, ATM serine/threonine kinase inhibitors; BETi, bromodomain and extra-terminal motif protein inhibitor; CDR132L, compound CDR132L; CAR-T, chimeric antigen receptor T-Cells. DIGIT-HF, DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure; DECISION, Digoxin Evaluation in Chronic heart failure: Investigational Study In Outpatients in the Netherlands Trial; D + Q, dasatinib and quercetin; 17-DMAG, 17-dimethylaminoethylamino-17-demethoxygeldanamycin; FOXO-DRI, fork head box O transcription factor 4-D-Retro-Inverso; HF-REVERT, Phase 2, multicentre, randomized, parallel, three-arm, placebo-controlled Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction After Myocardial Infarction. JAK-STATi, JAK-STAT signalling pathway inhibitors; miR(i), microRNA (inhibitors); p38-MAPKi, p38-mitogen activated protein kinase inhibitors; STACs, sirtuin activating compounds; SGLT2i, sodium/glucose cotransporter 2 inhibitors; PKMi, pyruvate kinase isozyme M2 inhibitors; TRAP-1-P, TRAP-1-proteolysis targeting chimera (PROTAC). Created in BioRender.com.

Senolytics are compounds that trigger apoptosis specifically in senescent cells. This approach is attractive, as deleting senescent cells may causally address the associated pathology at its root. Senolytic approaches take advantage of weak points in the senescence survival machinery either via pharmacological inhibition or suppression of immune system–evading surface receptors in senescent cells. The specific disadvantage of senolytics is a degree of toxicity in non-senescent cells. Furthermore, senolytics display effectiveness specific to certain cell lines.

As senolytic approaches carry an inherent risk of toxicity, suppressing SASP pathways without causing cell death may allow a safer and better tolerable approach for some patient groups. Senomorphic compounds target various molecular hubs that ameliorate the SASP, albeit sometimes at the cost of immune suppression.

Finally, epigenetic reprogramming aims to rejuvenate senescent cells by up-regulating the Yamanaka factors promising a deep, causal, and theoretically non-toxic approach. The main limitation of this approach is a potential risk of tumourigenesis, which may be circumvented with non-Yamanaka reprogramming on the level of non-coding RNAs such as micro-RNAs (miRs).

The overview of known anti-senescence compounds with various evidence levels of CVD benefit is seen in *Figure 2*. Data related to different compounds are summarized in *Table 1*.

Table 1 Summary of anti-senescence therapeutics and targets

Group	Compound names	Classification	Target	Development stage	Ref.
Cardiac glycosides	Digoxin digitoxin proscillaridin A K-strophanthin ouabain ouabagenin periplocin oleandrin	Senolytic	Na^+/K^+ pump, NOXA	In clinical use (digoxin and digitoxin)	66–72
Fibrates	Fenofibrate	Senolytic	PPAR-α	In clinical use	73,74
Aspirin	Acetylsalicylic acid	Senomorphic, senolytic; possible senescence-inducing	COX, possible other mechanisms in senescent cells	In clinical use	75–78
Statins	Atorvastatin simvastatin lovastatin	Senomorphic, senolytic	HMG-CoA reductase, possible other mechanisms in senescent cells	In clinical use	79–86
RAAS-blockers/ARNI	Ramipril losartan valsartan sacubitril	Senomorphic, senescence preventive	ACE, AR, MR, neprilysin, possible other mechanisms in senescent cells	In clinical use	79–96
Biguanides	Metformin	Senomorphic, senescence preventive	AMPK, possible other mechanisms in senescent cells	In clinical use	97–104
SGLT2i	Empfagliflozin dapaglilfozin canagliflozin	Senomorphic, senolytic	SGLT-2 AMPK PD-L1	In clinical use	105–112
BCL-2 family inhibitors	Dasatinib ABT-263 (navitoclax) ABT-737 A1155463 A1331852 BCL-xl PROTAC	Senolytic	Ephrins Src-kinase BCL-2 BCL-xl BCL-w	In clinical trials	13,23,25,28,50,113–139
BAX activator	BTSA-1	Senolytic	BAX	Pre-clinical	140
Natural compounds	Quercetin procyanidin C1 terreic acid daidzein	senolytic	BCL-2 family, possible other mechanisms in senescent cells	Pre-clinical or in clinical trials	141–147
Hsp-90 inhibitors	Geldanamycin tanespimycin 17-DMAG	Senolytic	HSP90	Pre-clinical or in clinical trials	148–152
BETi	Apabetalone	Senolytic	BET	In clinical trials	153,154

Continued

Table 1 *Continued*

Group	Compound names	Classification	Target	Development stage	Ref.
p53/p21 modulators	UBX0101 P22077 P5091 RG7112 FOXO-DRI	Senolytic	MDM-2 FOXO-4	Pre-clinical or in clinical trials	36,37,155–159
Immuno-clearance	PD-L1 inhibitors anti-NKG2D CAR-T anti-uPAR CAR-T anti-GPNMB vaccine anti-CD-153 vaccine	Senolytic	PD-L1, NKG2D, uPAR, GPNMB, CD-153	Pre-clinical	160–168
Rapalogs	Rapamycin everolimus tacrolimus	Senomorphic	mTOR	Pre-clinical, in clinical trials or in clinical trials	169–177
STACs	Resveratrol SRT-1720	Senomorphic, senescence-preventive	SIRT-1	Pre-clinical or in clinical trials	104,178–189
p38-MAPKi	UR-13756 BIRB-796 losmapimod	Senomorphic	p38, MAPK	Pre-clinical or in clinical trials	190–192
JAK-STATi	Rituximab	Senomorphic	JAK, STAT	Pre-clinical, in clinical trials or in clinical use	193–195
ATMi	KU-60019 KU-55933	Senomorphic	ATM	Pre-clinical	196–198
Metabolic modulators	K-35 K-27 TRAP-1 PROTAC	Senomorphic	PKM-2, TRAP-1, ALOX-5	Pre-clinical	199–201
Yamanaka factor modulators	Valproic acid CHIR-99021 E-616452 tranylcypromine forskolin	Reprogramming	Sox-2, c-Myc, Oct-4, KLF-4; GSK/WNT TGFßR-1 MAO cAMP	Pre-clinical	202–210
miRNAs	ASOs LNAs	Reprogramming	miR-22 miR-30-5p miR-34a miR-132	Pre-clinical or in clinical trials	209–224

ALOX-5, arachidonate 5-lipoxygenase; ARNI, angiotensin-receptor-neprilysin-inhibitor; ASO, anti-sense oligonucleotide; ACE, Angiotensin-converting-enzyme; ATMi, ATM serine/threonine kinase inhibitor; AR, Angiotensin receptor; BAX, BCL-2-like protein 4; BCL-2, B-cell lyphoma 2; BETi, bromodomain and extra-terminal motif protein inhibitor; cAMP, cyclic adenosine monophosphate; CD, cluster of differentiation; COX, cyclooxygenase; FOXO4, forkhead box protein O4; GSK, glycogen synthase kinase 3 beta; HMG-COA reductase, hydroxy-3-methyl-glutaryl-coenzyme A reductase; LNAs, locked nucleic acids; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; MAPKi, mitogen-activated protein kinase inhibitor; MR, mineralocorticoid receptor; mTOR, mammalian target of rapamycin; Na+/K+, sodium–potassium pump; NOXA, protein Noxa; NKG2D, natural killer group 2D receptor; KLF, Kruppel-like factor; p21, cyclin-dependent kinase inhibitor 1; PKM, pyruvate kinase; p38-MAPK, p38 mitogen-activated protein kinases; p53, cellular tumour antigen p53; PROTAC, proteolysis targeting chimera; RAAS, renin angiotensin aldosterone system; SIRT1, sirtuin 1; STACs, sirtuin-1-activating compounds; SGLT2i, SLC5A2 solute carrier family 5 member 2 inhibitor; TGFβR-1, TGF beta-receptor 1; TRAP-1, TNF receptor associated protein 1; WNT, wingless and Int-1 signalling factors; 17-DMAG, 7-dimethylaminoethylamino-17-demethoxygeldanamycin.

Of interest for accelerated clinical application, traditional CVD medication routinely used in the clinics may also exert anti-senescent effects, sometimes via multi-factorial mechanisms.

4. Anti-senescence therapies—already in clinical application?

4.1 Senolytics among approved CV drugs—cardiac glycosides and fibrates

Pre-clinical data show that cardiac glycosides exploit an increased Na^+/K^+ pump activity in senescent cells,[66] which was likely necessary to preserve membrane ionic stability in these enlarged cells. Furthermore, cardiac glycosides trigger NOXA-mediated apoptosis.[67] Digoxin causes cell death in senescent cells after *in vitro* treatment with doses within the therapeutic reference range measured in blood.[66,67] Digitoxin, another clinically approved cardiac glycoside, was almost exclusively toxic to senescent cells in one study,[67] but showed significantly less specificity to senescent cells in another.[66] Senolysis was also reported with other glycosides such as proscillaridin A, K-strophanthin, ouabain, ouabagenin, periplocin, and oleandrin.[66–68] Due to the well-described roles of digoxin and digitoxin in the treatment of heart failure and atrial fibrillation,[69] it is exciting to speculate whether the effects of these compounds stem from targeting senescence. A clinical trial (NCT06240403) aims to examine whether digoxin reduces senescence in human adipose tissues from patients with heart failure and diabetes. The distinction between various digitalis-derived substances may be highly relevant in the context of senescence, as not all cardiac glycosides were senolytic nor have optimal pharmacologic properties for the elderly. Digitoxin is typically preferred for use in older patients with renal dysfunction due to its more favourable pharmacokinetic profile.[70] Two large randomized multicentre clinical trials investigate potential benefit of digoxin and digitoxin in heart failure with reduced ejection fraction (HFrEF) (DIGIT-HF and DECISION).[71,72] By adding an anti-senescent component to their effect, some cardiac glycosides may witness an opening of a new chapter in their long history as cardiac therapeutics.

Fibrates are another group of known CVD-modifying drugs[73] with reported senolytic features.[74] In the context of removing senescent cells, fenofibrate acted as a senolytic by stimulating autophagic flux and activating peroxisome proliferator-activated receptor (PPAR)-α.[74] This effect has been examined in a model of rheumatoid arthritis, leading to decreased inflammation-related joint pathology.[74] It remains unknown whether fibrates remove senescent cells systemically and reduce CV senescent cell burden in a clinical setting.

4.2 Aspirin

Aspirin shows senomorphic activity by counteracting the loss of NO production in senescent endothelial cells[75] and improves ageing-related vascular relaxation in mice.[76] Aspirin has also senolytic effects in a study exploring long-term extra-cardiac adverse effects of doxorubicin.[77] Another study, however, reported an opposite, senescence-inducing effect of aspirin on cancer cells.[78]

4.3 Statins

Statins are a staple of lipid-lowering therapy and CV event prevention.[79] These drugs show a complex relationship with senescence. Atorvastatin prevents the onset of senescence in endothelial progenitors,[80] while simvastatin acts as a senomorphic and antagonizes the pro-inflammatory SASP in senescent fibroblasts in breast cancer.[81] These effects may stem from the SASP-activating mevalonate pathway[82] or restricting cholesterol lysosomal partitioning that supports the SASP.[83] Simvastatin, atorvastatin, and lovastatin, but not pravastatin, are senolytic and trigger senescent cell death at high doses.[84] It thus may be speculated that the formation of presumably senescent foam cells[85] in atherosclerotic plaques gets prevented by intensive statin therapy. On the other hand, statins sensitize cells to senescence after radiation.[86] Due to the complex roles of lipids in senescence, statins may have situationally specific effects in senescent cells.

4.4 Renin-angiotensin-aldosterone system blockers

Inhibition of the renin-angiotensin-aldosterone system (RAAS) system is an essential element of primary and secondary CVD prevention, as well as heart failure therapy.[79] Cardiac, coronary, and renal senescence was increased in arterial hypertension.[87] Angiotensin 2 receptors (AT2Rs) were over-expressed in ageing rodent hearts[88] and senescent kidney cells.[89] Angiotensin-converting enzyme (ACE) and AT2R receptor blocker (ARB) attenuated markers senescence in cultured vascular smooth muscle cells (VSMCs) and rat kidneys.[90,91] ACE and ARB also reduced omics signatures of senescence in cohorts of heart failure and naturally ageing patients.[92,93] Valsartan is combined with neprilysin in heart failure therapy, where neprilysin additionally reduces senescence biomarker insulin-like growth factor-binding protein-7 (IGFBP-7) in heart failure with preserved ejection fraction (HFpEF) patients when compared with the ARB alone.[94] Senescence was induced in kidney fat tissue via the mineralocorticoid receptor (MR), which is preventable via co-treatment with MR blockers.[95,96] It remains unclear whether RAAS inhibition directly affects senescent cells or prevents hypertension-induced senescence. Either way, suppressing senescence appears to constitute an important aspect of approved CV drugs.

4.5 Metformin

As a broadly implemented anti-diabetic medication reducing CV mortality in Type 2 diabetes,[97] metformin was examined for anti-senescence effects in multiple experimental models. Metformin suppresses the SASP by inhibiting pro-inflammatory nuclear factor-κB (NF-kB) signalling,[98] while pharmacologically mimicking caloric restriction through sirtuin 1 (SIRT1) AMP-activated protein kinase (AMPK) activation and depression of insulin-signalling through IGF1.[99,100] Metformin also improves ROS detoxification through increased endoplasmic glutathione peroxidase 7 expression and improves mitochondrial function.[101] In pre-clinical *in vivo* models, metformin exerts anti-ageing effects on naturally ageing in mice by improving their lifespan and healthspan.[99] This led to the initiation of the Targeting Aging with Metformin trial specifically examining anti-ageing effects of metformin.[102] Despite its pleiotropic effects at suppressing senescence, the positive effect of metformin on CVD outcomes in non-diabetics is debateable.[103] Early-generation Sirtuin (SIRT)-1 agonists also failed to provide anti-senescence effects outside metabolic syndrome models.[104] Metformin may be similarly limited to the metabolic milieu of diabetes-related cellular senescence.

4.6 Sodium glucose linked transporter 2 inhibitors

Sodium glucose linked transporter 2 inhibitors (SGLT2is) were initially effectively used for the treatment of Type 2 diabetes mellitus. The indications for SGLT2i are now widely expanded outside diabetes. Dapagliflozin and empagliflozin are used for the treatment in all classes of heart failure (HFrEF, heart failure with mildly reduced ejection fraction, and HFpEF).[105–108] Canagliflozin also improves clinical outcomes in diabetics with heart failure,[109] likely also being effective irrespective of diabetes status.[109]Canagliflozin has multi-faceted anti-senescence effects via metabolic reprogramming through AMPK activation.[110] This effect additionally led to PD-L1 down-regulation in senescent cells, enabling immune clearance of senescent cells resulting in a decreased senescence burden in progeria mice, mice on a high-fat diet, and apolipoprotein E-knockout mice.[110] Dapagliflozin counteracted cardiomyocyte senescence via angiopoietin-like 4 protein in a model of diabetic cardiomyopathy.[111] SGLT2i also demonstrated protective effects in diabetic kidneys, which may be attributed to senescence amelioration by dapagliflozin.[112] Of note, different SGLT2is show varying potency in modulating cardiac fibrosis pathways, and it should be explored whether this also applies to anti-senescence effects.[225]

Moving beyond approved CV therapeutics with reported anti-senescence effects, potent compounds targeting cellular senescence were found among drugs in the oncology field.

5. Anti-senescence drugs outside cardiology—opportunity for repurposing

5.1 Senolytics—BCL-2 family inhibitors

The development of senolytics as whole started with a tyrosine kinase inhibitor used for haematological malignancies—dasatinib. In combination with an over-the-counter (OTC) available flavonoid compound quercetin, the combination of dasatinib and quercetin (D + Q) inhibited the family of anti-apoptotic factors BCL-2, ephrin, and SRC kinases.[113,114] D + Q synergistically triggers programmed cell death in multiple cell lines (murine embryonic fibroblasts, human umbilical vein endothelial cells (HUVEC), and pre-adipocytes).[113,114] In a murine model of myocardial infarction, female mice treated with D + Q exhibited improved left ventricular ejection fraction.[115] D + Q mildly improves ageing-associated left ventricular ejection fraction (LVEF) decline in aged mice.[113] D + Q heightened cardiac regenerative capacity[116] and vasomotor function, albeit without reducing atherosclerotic plaque burden.[117] Moving to other age-associated diseases, D + Q displays anti-fibrotic activity in *in vivo* and *ex vivo* models of lung fibrosis.[25,118] D + Q also alleviates organ dysfunction in other pre-clinical models of ageing-associated diseases and common CV comorbidities, including diabetic nephropathy,[119] metabolic syndrome,[120] and intervertebral disc degeneration.[121] Likely due to its cumulative effects in multiple organs, D + Q extends the physiological lifespan of mice.[122]

D + Q was introduced into the early phase clinical trial milieu as a senolytic. Early feasibility trials in idiopathic pulmonary fibrosis,[123,124] diabetic nephropathy,[125] Alzheimer's disease,[28] and osteopenia[23] are under-powered for the evaluation of clinical outcomes but show tolerability with trends towards improved physical fitness and reduction of senescence, SASP, and common disease biomarkers. It remains unknown whether D + Q provide beneficial effects in the setting of CVD. An approval for dasatinib in a setting of heart failure may be challenging due to reported drug-associated precapillary pulmonary hypertension[126] and pleural effusions.[127] A potential solution is intermittent dosage of D + Q.[114] Alternatively, quercetin monotherapy may suffice and is being clinically evaluated for anti-senescence and anti-inflammatory effects after coronary bypass surgery (NCT04907253). Quercetin-laden nanoparticles may enhance compound delivery and anti-senescence effects.[128]

More precise targeting of BCL-2 family proteins is possible via an experimental compound ABT-263 (navitoclax) in early trials for treating advanced solid tumours and haematologic malignancies.[129,130] This compound eliminated senescent cells through the inhibition of BCL-2, BCL-xl, and BCL-w.[131] ABT-263 stabilized atherosclerotic plaques,[132] ameliorated ischaemia-reperfusion injury,[13,133] and improved survival after myocardial infarction in mice.[134] Navitoclax was well tolerated and reduced senescence markers in primates.[135] Additional BCL-2-family inhibitors such as ABT-737, A1155463, and A1331852 also showed senolytic properties.[50,136]

Targeted inhibitors of the BCL family have limitations for clinical implementation in the CV setting. Navitoclax causes thrombocytopenia due to BCL-xl inhibition.[137] Aiming to increase the specificity of this senolytic towards senescent cells, galacto-conjugation of navitoclax significantly reduces toxicity towards platelets.[138] Improvements have also been achieved by localized cardiac application of navitoclax.[133] Initiating intrinsically targeted autophagy of BCL-2 via proteolysis targeting chimaeras also produces less off-target effects.[139] Another strategy possibly sparing thrombocytes may be achieved by shifting the survival machinery against BCL-2 by pharmacological BCL-2-associated X-protein activation via compound BTSA-1. This approach is beneficial in experimental pulmonary fibrosis.[140]

Utilizing natural compounds such as fisetin, a flavonoid polyphenol, is an attractive option to introduce senolytics in the clinic. Fisetin removes senescent cells and increases lifespan of in progeria mice while reducing senescent cell burden *ex vivo* in human adipose tissue.[141] Fisetin decreases arterial wall stiffness.[142] Fisetin also restricts renal fibrosis,[143] improves muscular performance in muscular dystrophy,[144] and reduces corona virus–related mortality in elderly mice.[145] A presumed mechanism of action for fisetin is senolysis through the inhibition of the BCL-2/BCL-xl/BCL-w survival network.[136] The therapeutic application of fisetin is challenging due to its low water solubility and limited bioavailability. This may be circumvented by utilizing nanocarriers, possibly in combination with quercetin.[128] Procyanidin C1, terreic acid, and daidzein are additional natural compounds with reported senolytic effects.[146,147] Special care is needed with natural and OTC compounds, as they may have unreliable safety or pharmacokinetic profiles, requiring more stringent trials before approval for a major CV indication.

5.2 Senolytic autophagy modulators

Modulating autophagy also causes senolysis. Heat shock protein (HSP) 90 inhibitors are compounds in clinical development for treatment of various tumours.[148] Geldanamycin, tanespimycin, and particularly the better water-soluble variant 17-DMAG selectively eliminate senescent human IMR90 and WI38 cells *in vitro* and extend longevity of mice.[136] Another HSP90 inhibitor XL888 reduces senescence in *ex vivo* human fibrotic lung slices.[149] HSP-90 inhibition attenuates Angiotensin II–related vascular remodelling[150] and cardiac hypertrophy.[151] It is unknown whether these effects on experimental CVD stem from eliminating senescent cells. Early-generation HSP-90 inhibitors display major gastro-intestinal adverse effects, sometimes causing trial termination.[148] Improvements in tolerability are a prerequisite before implementation for CV indications.

Alternative strategies exploiting autophagy utilized bromodomain and extra-terminal domain (BET) family protein degraders, which trigger senolysis through a combined activation of (macro)autophagy and overload of DNA damage repair. This shifts the survival balance towards apoptosis in senescent fibroblasts and showed benefit in murine tumour models.[152] In a clinical context of CVD, a BET inhibitor apabetalone failed to improve composite major adverse CV events as a primary endpoint in diabetics after acute coronary syndrome in a large Phase III trial.[153] A *post-hoc* analysis shows signal towards reductions of heart failure hospitalization.[154] Data correlating apabetalone with anti-senescent effects are currently lacking.

5.3 Senolytic p53 modulators

Manipulating p53 as a major modulator of apoptosis is an attractive strategy to eliminate senescent cells. Several strategies tackling this central regulator of cell survival have emerged. Murine double minute 2 (MDM-2) E3 ligase causes p53 degradation by priming it for proteasomal degradation.[36] Inhibition of MDM-2 and consequent p53 activation by compound UBX0101 trigger apoptosis in senescent chondrocytes,[155] but failed to provide benefit in a Phase II trial in knee osteoarthritis.[156] Activating MDM-2-mediated p53 degradation through compounds P22077 and P5091 achieves senolysis through similar mechanisms.[157] Another MDM-2 inhibitor RG7112 also allows senolysis.[158]

Another strategy of senolysis via exclusion of p21 from the nucleus by preventing its interaction with p53 and FOXO4 through a synthetic peptide (FOXO-DRI) caused counteracts doxorubicin-induced senescence and renal function loss in aged mice.[37] Due to its complex roles, activating p53 via MDM-2 inhibition may also have senescence-inducing effects.[159]

5.4 Senolysis via the immune system

An improvement of immune surveillance of senescent cells and the consequential CD8+ T-cell–based senolysis was achieved by PD-L1-PD inhibition.[160] This approach is beneficial in naturally ageing mice, as well as premature senescence-associated non-alcoholic steatohepatitis. Immune checkpoint inhibition was associates with rare but often serious cases of myocarditis.[161] Further research homing in checkpoint inhibition to

senescent cells with greater specificity is necessary before clinically advancing this potentially cardiotoxic treatment.

Macrophages may be enticed to remove senescent cells by inhibiting CD-47 as a 'do not eat me' signal in senescent cellular populations.[162] 4N1Ks is a thrombospondin 1-mimetic and CD-47 inhibitor that causes senescent cell death already without involving the innate immunity, implicating additional importance of CD-47 downstream signalling for senescent cells.[163]

Senescent cells evade removal through NK-cells via the up-regulation of NKG2D; this could be resolved by injecting anti-NKG2D chimeric T-cell receptor cells (CAR-T) cells.[164] This therapy reduces chronic inflammation, improves fitness in ageing mice, and is well tolerated in primates. Another CAR-T strategy targeting the urokinase receptor (uPAR) in senescent cells relieves liver fibrosis and improves survival of lung carcinoma mice under chemotherapy.[165]

Vaccinating against cellular senescence showed promise in reducing ageing-related pathologies. A vaccine against the transmembrane glycoprotein NMB (GPNMB) reduces atherosclerotic plaque burden and improves lifespan of male progeria mice. The vaccination ameliorates metabolic dysfunction in wild-type mice on a high-fat diet with improved performance in comparison with navitoclax and D + Q, while lacking thrombocytopenia typical for navitoclax.[166] Similar metabolic benefit is seen in mice immunized via a CD-153 vaccine targeting senescent T cells.[167] Vaccination by injecting entire senescent carcinoma cells, triggering a subsequent T-cell response, suppresses tumour growth and metastasis in mice, while effects of the CV system remain unknown.[168]

5.5 Senomorphic (anti-SASP) therapies

Multiple drugs named senomorphics are used in the clinics outside CVD prevention. These compounds ameliorate the SASP. The advantage of senomorphic therapies is based on extensive modulation molecular networks in senescent cells, thus simultaneously reducing the senescence-associated expression of multiple pro-inflammatory cytokines and comprehensively addressing chronic inflammation. This may be an advantage of senomorphics in comparison with contemporary anti-inflammatory strategies that tackle singular pathways out of a complex network and reach a limited effect.[1] The main disadvantage of senomorphics is the lack of a permanent solution for accumulated senescent cells, which can be achieved by their removal with senolytics. Furthermore, they may have immune-suppressive features. However, senomorphic therapies are expected to show no significant toxicity and would thus be more suitable for some patient populations.

5.6 Senomorphic rapalogs

Rapalogs (rapamycin, everolimus, and tacrolimus) are known in daily CV clinics as components that prevent in-stent restenosis of drug-eluting stents via local anti-proliferative and immune-suppressing effects due to mTOR inhibition.[169] mTOR also plays an important role in maintaining the SASP in senescent cells by promoting NF-kB signalling with downstream IL1A expression.[170] Heterogenous mouse population systemically treated late in life with rapamycin show an ameliorated ageing phenotype and a prolonged lifespan.[171] Short-term treatment with rapamycin decreases cardiac hypertrophy and stiffness even after cessation of therapy.[172] Early human trials show acceptable tolerability of rapamycin in older individuals.[173,174] Data specifically showing positive CV effects of systemic rapamycin or its derivatives outside pulmonary hypertension[175] are lacking. Rapamycin-induced immune suppression and hyperlipidaemia are a matter of concern in CV patients.[176,177]

5.7 Senomorphic sirtuin-1-activating compounds

SIRT-1 depletion is a component of the molecular signature of ageing and heart failure.[178] Resveratrol was the initial SIRT-1-activating compound that counteracted the SASP by inhibiting NF-kB[179] and NLRP-3 signalling in the heart.[180,181] These anti-SASP effects show benefit in *in vitro* models of doxorubicin-[182] and ischaemia-induced cardiomyocyte senescence,[180] as well as in VSMC isolated from aged primates.[183] Resveratrol showed anti-ageing effects only in mice fed with a high-calorie diet[104,184] and demonstrated poor bioavailability in humans.[185] Furthermore, higher doses of resveratrol induce senescence.[186] Several more potent resveratrol derivatives have been developed to address these concerns.[187] Yet, data from several small-scale trials failed to demonstrate consistent benefit and struggled with reliable pharmacokinetics,[188] while increasing CVD biomarkers such as soluble vascular cell adhesion molecule-1 and total plasminogen activator inhibitor.[189]

5.8 Senomorphic p38-MAPK inhibitors

Stress sensing p38-MAPK was activated in senescent cells, and its inhibition improved skeletal muscle regeneration in aged mice.[190] Pharmacological suppression via compounds UR-13756 and BIRB 796 of this pathway repressed pro-inflammatory SASP cytokines.[191] In a clinical setting, inhibition of p38 via losmapimod did not improve outcomes in 12 weeks after myocardial infarction.[192] Timing is likely a key when applying senomorphics in the setting of myocardial infarction (see the '8. Discussion' section).

5.9 Senomorphic janus kinase /STAT inhibitors

Janus kinase (JAK) 1 and JAK-2 inhibition counters sterile chronic inflammation in a murine model.[193] Rituximab inhibits JAK-2/STAT-3 with downstream reduction of ROS and ameliorated cardiomyocyte senescence in a model of septic cardiomyopathy.[194] Preliminary data from rheumatology studies indicated a possible increase of CVD events under JAK inhibitor tofacitinib, prompting issue warnings from the US Food and Drug Administration and the European Medicines Agency.[226] Subsequent analyses show no increased CVD risk[226] with JAK inhibitors. JAK inhibition is proposed for use[227] to address low-grade inflammation in atherosclerosis, as senescence-associated phenomenon.[1,15] Upstream antagonization of the JAK-STAT signalling via IL-11 antagonization also counteracted senescence, improving life- and health span of mice.[195]

5.10 Senomorphic ATM inhibitors

Ataxia-telangiectasia mutated (ATM) serine/threonine kinase acts as a key coupling agent between the DNA damage response and cytoplasmic NF-kB activation, which in turn facilitated the SASP gene expression.[196] Furthermore, ATM hinders lysosomal acidification and mitochondrial maintenance.[197] This made ATM a target to counteract the SAS. ATM-inhibiting compounds KU-60019 and KU-55933 suppress senescence-associated inflammation.[197] Genetic ATM deficiency hinders the physiological roles of senescence fibroblasts after myocardial infarction and reduced angiogenesis, leading to worsened heart failure,[198] again indicating that therapeutic timing is a key for anti-senescence strategies.

5.11 Metabolic senomorphic agents

Fine-tuning the metabolism of senescent cells enables anti-SASP effects. Senescent cells accumulate pyruvate kinase isozyme M2 (PKM-2), which disabled a physiological glycolytic flux and drives premature cellular ageing. Pharmacological dispersal of PKM-2 aggregates via compounds named K35 and K27 repressed the SASP and delayed ageing in progeria and naturally aged mice.[199] Inhibition of lipid-based signalling in senescent cells provides anti-fibrotic effects in lungs.[200] PROTAC-mediated targeting of TNF receptor-associated protein 1 (TRAP-1), a regulator of anaerobic glycolysis in senescent VSMCs, reduced SASP and ameliorated atherosclerosis in mice.[201] Specific targeting of metabolism in cellular senescence may be a novel frontier to supplement current broad metabolic CVD reducers.

6. Epigenetic reprogramming

Reverting the epigenetic clock[228] in senescent cells towards a rejuvenated non-senescent state can be achieved by short-term cyclic re-activation of

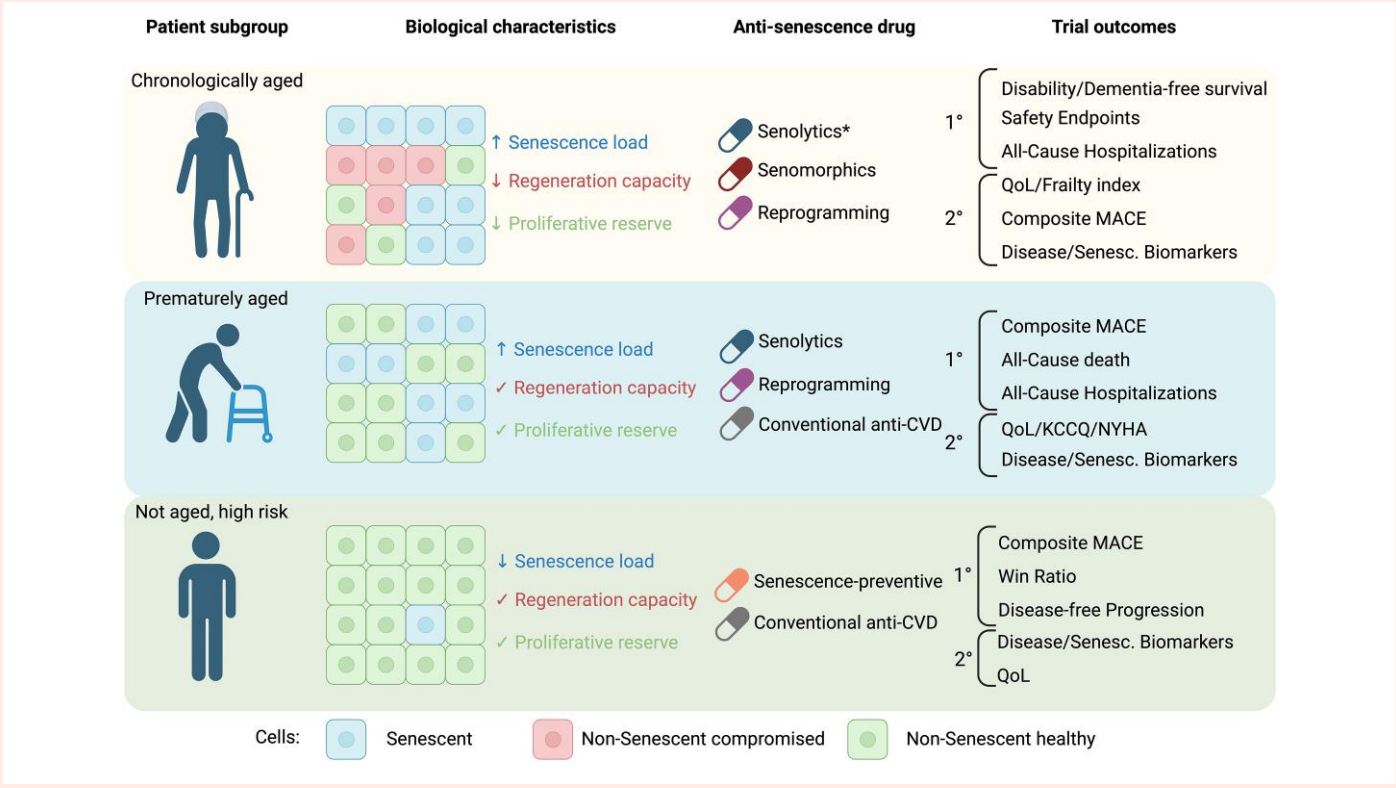

Figure 3 Adaptations to clinical trial design for anti-senescence therapeutics. 1°, primary outcome; 2°, secondary outcome; KCCQ, Kansas City Cardiomyopathy Questionnaire; MACEs, major adverse cardiovascular events (non-fatal stroke, non-fatal myocardial infarction, cardiovascular hospitalization, and cardiovascular death); NYHA, New York Heart Association Functional Classification; QoL, quality of life. *Special care needs to be taken when selecting chronologically aged patients for senolytic trials by considering patient goals, regeneration capacity, frailty, and tolerance for possible adverse effects. Created in BioRender.com.

pluripotency genes Sox2, C-Myc, octamer-binding transcription factor (Oct) 4 and Kruppel-like factor (KLF) 4.[202–205] This approach slows ageing in murine progeria[203] and reverses vision loss in naturally aged mice.[206] Senescent cells extracted from the elderly required additional overexpression of homeobox protein NANOG (NANOG) and Lin-28 homologue A (LIN-28).[207] Multiple cocktails of drugs can reportedly achieve this affect, extending the lifespan of progeria mice. For example, valproic acid, CHIR-99021 [glycogen synthase kinase 3 inhibitor/wingless and Int-1 (WNT) activator], E-616452 (transforming growth factor beta-receptor 1 inhibitor), tranylcypromine (monoamine oxidase inhibitor), and forskolin (cyclic AMP activator) together revert the transcriptome of senescent cells.[208] 3-Deazaadenosine is another an epigenetic-modifying anti-senescence compound.[209] However, forcing stemness in senescent cells may cause aggressive forms of malignancy.[210] Furthermore, complex interactions from drug cocktails are challenging in respect to early clinical trial design.

Fine-tuning epigenetics outside Yamanaka factors via non-coding RNAs such as miRs is an alternative approach to reprogramming.[211] miR-30–5p drove senescence via RNA-binding protein TIA-1 by orchestrating downstream mitochondrial dynamics, and its inhibition can reduce senescence markers.[212] Differing effects of the miR-30 family has been shown in heart failure models.[213,214] Antagonizing miR-22[215] and miR-34a[216] reduces adipocyte senescence. miR-22 inhibition also attenuates metabolic disorders via targeting senescence in mice.[215] miR-21 was a critical regulator of cardiac fibrosis, and its inhibition conferred to improved heart failure in experimental models.[217] This miR could be a major paracrine inducer of senescence of endothelial cells, demonstrating a wider inter-cellular role of these non-coding RNAs.[218,219] Of note, senescent macrophages influence fibroblasts via secreted miR-132.[220] The beneficial effects of the miR-132 inhibition may be in part explained by anti-senescence effects. miR-132-inhibiting compound CDR132L has entered the clinical trial setting in the HF-REVERT trial, opening a new era in heart failure therapeutics.[221–224]

7. Towards senescence-orientated clinical trial design

7.1 Patient selection and choice of anti-senescence drug

Significant lessons can be acquired by drawing from abovementioned early experiences from clinical trials of anti-senescence compounds, as well as long-lasting efforts in the field of conventional anti-CVD therapeutics. Based on current knowledge, we anticipate three patient groups where anti-senescence therapies can build upon current therapies to improve outcomes: not aged (but at risk of premature senescence), prematurely aged, and chronologically aged patients. All these patient groups may require different trial designs and specific choices of anti-senescence drugs to detect positive outcomes, which are shown in the *Figure 3*.

The first group that can benefit from anti-senescence therapies are chronologically aged individuals, the classical cardio-geriatric patients. This group often presents with specific treatment preferences, with a focus on quality of life, decreased hospitalizations, and hospital follow-ups, as well as reduced disability.[229] The chronologically old are heterogenous and characterized by various comorbidities as competing risks, altered drug pharmacokinetics or pharmacodynamics, and often featuring polypharmacy.[230] To improve the statistical robustness by homogenizing these confounders, current CVD clinical trials often exclude the chronologically

old.[231] Further adding to the heterogeneity of chronologically old patients, numbered age may not strictly correlate with senescence burden.[1] Trials within this group would include individuals with depleted regeneration capacities and significant frailty.[232] As such, the primary focus should be placed on disability-related or all-cause outcomes with a special focus on tolerability. Non-toxic senomorphic or reprogramming approaches could be optimal for highly frail individuals. Chronologically aged patients with a high senescent cell load could also profit from senolytic therapies. The toxic adverse effects of senolysis may be circumvented by applying a 'hit and run' approach and/or via localized delivery through percutaneous intervention. As senescent cells take long periods to accumulate and do not proliferate, senolytics could be applied via regimes with long off-drug periods between doses. These spread-out regimes may confer an advantage in comparison with senomorphic and reprogramming agents, which likely must be given continuously and contribute to polypharmacy. An alternative strategy to evade systemic toxicity may be an *ex vivo* rejuvenation of isolated bone marrow–derived angiogenic cells via senolytics and subsequent autologous re-injection, as suggested for ischaemic cardiomyopathy.[1] Special care needs to be taken when selecting chronologically aged patients for senolytic trials by considering patient goals, regeneration capacity, frailty, and tolerance for possible adverse effects. It is important to monitor and learn from experiences of ongoing trials with senolytics (overview available at https://www.tgerosci.net).

The second group to be selected for anti-senescence trials are individuals with accelerated biological ageing. However, conventional CV therapies already substantially reduce death risks; therefore, any additional effects of anti-senescence drugs would be challenging to detect. As these therapies should confer multi-organ benefits, this may be circumvented by utilizing composite endpoints combining CV and non-CV events. More aggressive treatment of senescence via senolytics or reprogramming can be beneficial in this patient group but requires patients with substantial regenerative capacities to repair ensuing cell loss or to respond to reprogramming. Systemic or local cellular telomeres length measurements and multi-omics approaches (see below) may guide such trials.

The third patient group that can profit from anti-senescence approaches are those with a low initial senescence burden but at risk of rapidly accumulating senescent cells. This risk originates from genetic or acquired factors. The most drastic examples of genetic influences on ageing are progeria syndromes (Hutchinson–Gilford progeria, Werner Syndrome, and other laminopathies)[233] where patients die of myocardial infarction or stroke at an early age.[234] More subtle genetic variations of many other genes (e.g. encoding Phospholipase C Epsilon 1, FOXO-3, and BPI fold containing family B4) contribute to premature CV ageing.[235–237] Conventional acquired factors such as high-calorie diets, smoking, arterial hypertension, and dyslipidaemia also accelerate senescence.[1] As this patient group starts with a relatively low death risk and comparably less organ dysfunction, longer follow-ups with composite outcomes would be needed in prospective trials to detect benefits of anti-senescence interventions. This patient group would require drugs with excellent tolerability and no toxicity, which may be an issue for senolytics. Long-term safety is essential, which can be problematic for some reprogramming therapies that may confer malignancy risk.

7.2 Biomarkers of senescence burden

The development of senescence biomarkers is instrumental for the identification of proper patient populations and monitoring the effects of anti-senescent therapies. Several strategies have been proposed.

Individual markers may serve as a simple and potentially cost-effective method of detecting senescence. Alpha-Klotho expression is lost in senescence.[238] This feature tracks the anti-senescent effects of D + Q, where the senolytic therapy restores urinary alpha-Klotho in the urine of idiopathic pulmonary fibrosis patients.[238] Patients responding well to heart failure therapy show improved blood alpha-Klotho levels[239]; it remains however unknown if this biomarker is specific and chemically stable enough for routine clinical use. Another promising biomarkers are signalling lipids called oxylipins, which are specifically released by dying senescent cells in response to senolytic therapy in mice.[240] Leucocyte telomere length is a biomarker of replicative senescence associated with heart failure,[241,242] albeit with large inter-personal variation and little correlation to other forms of senescence.[243] Tracking senescent immune cell populations may be another surrogate marker for total body senescence burden. Some of these populations have already shown promise as biomarkers of CVD. Leukocytes expressing p66Shc are indicators of instable coronary disease,[244] and senescent T-EMRA cells predict CV mortality within the chronologically aged.[245] IGFBP-7,[94] Beta-2-microglobulin, and oxidated vimentin are additional proposed specific biomarkers of senescent cells.[246,247] As cardiac biopsies are unlikely to be routinely used for assessing senescent cell burden due to safety risks and low representability of rare senescent cell populations in small samples, accessible tissues such as skin or fat can aid tracking senescent cell burden. Some classical senescence markers (p16 and p21) may not be applicable for all senescent cell types in cardiac histological sections (particularly in cardiomyocytes, see the '8. Discussion' section). Senescence-associated β-galactosidase (SAβG) staining of increased lysosomal activity in senescent cells can be useful in frozen section analysis of fresh biopsies but may show false positivity in macrophages.[13] Markers of DNA damage (histone γ-H2AX) have been also used to detect senescent cells but may miss some forms of senescence such as pure mitochondrial dysfunction-associated senescence (MIDAS).[115] The major limitation of one-marker approaches is that senescence cells lack specific defining singular molecules. They rather show a pattern of multiple wider perturbations on an epigenetic, proteomic, metabolomics, and post-translational level. These can be detected by multiplex approaches.

Multiplex approaches are thus increasingly used to detect these complex features of cellular ageing in blood.[46] Multiple epigenetic clocks measure DNA methylation patterns associated with ageing and could predict CV and all-cause mortality.[248] Proteomics reveals an array of SASP markers as an independent risk factor for heart failure.[93] Even higher resolution approaches integrate multi-omics, clinical characteristic, and machine learning.[92,249,250] These can predict the progression of atherosclerosis in asymptomatic individuals,[251] which is intriguing for designing preventive drug trials with patients displaying low senescence burden.[9] The major limitation of these approaches are large costs, but these will likely decrease and enable refined strategies in clinical trial design.[252]

8. Discussion

Several limitations challenge the field of cellular senescence.

Pre-clinical and clinical researches face a complex cellular machinery behind senescent cells, and there is much to be learned about the roles of senescent cells both in physiological conditions and CVD pathophysiology. A major current limitation is a lack of specific markers for senescent cells, which is of particular significance in cardiac tissues. For instance, recent guidelines[253] on histological detection recommend classical senescence markers (high expression of p16 and p21; negative proliferation markers such as PCNA; loss of lamin B1 with nuclear enlargement, HMGB-1 nuclear loss, DNA damage markers and telomere-associated DNA damage foci, senescence-associated distension of satellites, phosphorylated STAT-3; and Perlipin 2-positivity). These markers are not fully validated in cardiac tissues, and some are not correlated with clinical outcomes (as reported for lipofuscin).[254] Cardiomyocytes are the dominant cell type in cardiac tissues and have features that hinder the application of some standard senescence markers. For example, p16 and p21 are a part of the physiological cell cycle arrest machinery in these cells.[255] Although increased overall expression of p16 and p21 plays molecular roles in cardiomyocyte senescence,[256] their presence in physiological arrest decreases specificity and does not define cardiomyocyte senescence. Senescence cardiomyocytes are characterized by senescence-associated molecular perturbations (*Figure 1*) and the SASP, as cardiomyocyte proliferation capacity remains controversial. Similar challenges are faced when studying macrophages, as they show significant overlap between senescence markers and physiological features of activity in these cells, as demonstrated with false positive SAβG staining.[65]

Furthermore, pre-clinical data show that senescent cells of different types are vastly heterogenous in terms of function, intra-cellular expression patterns, and the SASP. First, some senescent cells have physiological and beneficial roles, particularly in tumour suppression, tissue repair, and embryologic development.[1] Helper-senescent cells (H-subtype) can be broadly differentiated from deleterious senescent cells (D-subtype).[257] There are some indications that senolytics mostly affect D-cells, but this concept needs more research in the CVD setting.[257] Secondly, the senescent phenotype depends on the trigger of senescence. Dominantly DNA damage–associated senescence has a different SASP compared with MIDAS.[258] Senescence *in vivo* likely has multiple concurrent and less delineated senescence triggers.[1] Thirdly, the SASP profile depends on the cell types, as discussed previously.[1] Some anti-senescence therapies show cell type–specific effects, particularly senolytics.[1] The development of single-cell omics methods will provide a higher-resolution view into these intricacies and possibly guide cell-orientated therapeutic approaches.

For the clinical applications of anti-senescence therapies, timing and choice of drug class is essential. As senescence plays a role in acute tissue repair, applying senomorphics too early after myocardial infarction may repress wound healing, without permanently addressing persisting cellular senescence as a trigger of chronic maladaptive modelling.[256] However, senolysis leads to improvements in acute myocardial infarction in pre-clinical models.[133,134] The elimination of senescent cells via senolytics does not permanently repress the senescence molecular programme.[133,134] Senomorphics still may be a viable alternative to senolytics in a sub-acute to chronic timepoint after myocardial infarction for some patients, as discussed above and shown in *Figure 3*.

9. Conclusion

Anti-senescence therapies represent a novel frontier for the treatment of CVD. Multiple options have emerged among this rising drug class. However, a change in current clinical trial paradigms is likely needed to translate these treatments to patients.

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Data availability

No data were generated in this manuscript.

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