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Pharmacological Strategies to Retard Cardiovascular Aging

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Abstract

Aging is the major risk factor for cardiovascular diseases (CVD), which are the leading cause of death in the United States. Traditionally, the effort to prevent CVD has been focused on addressing the conventional risk factors, including hypertension, hyperglycemia, hypercholesterolemia, and high circulating levels of triglycerides. However, recent preclinical studies have identified new approaches to combat CVD. Calorie restriction has been reproducibly shown to prolong lifespan in various experimental model animals. This has led to the development of calorie restriction mimetics and other pharmacological interventions capable to delay age-related diseases. In this review, we will address the mechanistic effects of aging *per se* on the cardiovascular system and focus on the pro-longevity benefits of various therapeutic strategies that support cardiovascular health.

Keywords

cardiovascular diseases; aging; calorie restriction; pharmacological strategies; prevention

I. Introduction

The population in the Western world is aging at an unprecedented rate. The substantial increase in life expectancy is associated with significant age-related cardiac, arterial and microvascular disease burden. In the United States, ischemic heart disease and stroke are the

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leading cause of death[1] (see definition in Table 1) and their incidence exponentially increases with advanced age. Epidemiological studies clearly show that aging itself is the major risk factor for cardiovascular (CV) and cerebrovascular diseases. Yet, most of the research efforts on prevention of these diseases have ignored the mechanisms underlying cardiac and vascular effects of aging, and have focused, instead, on the development of interventions that target conventional cardiovascular risk factors (e.g. hypertension, high circulating levels of glucose, cholesterol and triglycerides). In this review, the mechanistic effects of aging *per se* on the CV system are considered. The possible benefits of therapeutic strategies that have the potential to improve CV function in the elderly and delay the onset of age-related CV diseases (CVD) are also discussed (see summary in Table 2 and Figure 1).

II. Mechanisms of cardiovascular aging: from oxidative stress and chronic low grade inflammation to structural and functional impairment

1) Cardiac aging

A continuum of progressive cardiac structural and functional alterations occurs with age in humans and laboratory animals, including increases in collagen levels, cardiac hypertrophy,[2] decreased heart rate and diastolic filling rate,[3] and impaired left ventricle function (reviewed recently in [4]). The molecular and cellular mechanisms of cardiac aging involve macromolecular damage and mitochondrial oxidative stress,[4–6] perturbation of proteostasis,[7] age-dependent declines in autophagy and ubiquitin proteasome degradation,[8,9] stem cell dysfunction,[10,11] extracellular matrix remodeling,[12,13] increased apoptosis,[14] impaired bioavailiability of nitric oxide (NO),[15] poly(ADP-ribose) polymerase 1 (PARP-1) activation and cellular energetic dysfunction,[16] activation of the renin-angiotensin-aldosterone system, and age-related low-grade sterile inflammation.

2) Vascular aging

Changes in the structure and function of the large arteries that occur throughout life include diffuse intimal and medial thickening and increased stiffness of wall components, a cause of reduced distensibility of central arteries.[17,18] Age-related chronic inflammation in the large arteries promote the pathogenesis of atherosclerotic diseases (stroke, peripheral artery disease, and myocardial infarction), which are a leading cause for mortality and morbidity in the elderly.

The microcirculation, with a total length of ∼100,000 km, is the most ubiquitous organ system, which envelops virtually every cell in the human body and whose age-related alterations fundamentally impact the function of every organ. The mechanisms by which microvascular alterations contribute to age-related functional decline of multiple organ systems include microvascular endothelial dysfunction,[19,20] microvascular rarefaction,[21,22], dysfunction of local vasoregulatory mechanisms including impaired shear stress-induced vasodilation,[19] myogenic autoregulatory dysfunction,[23–26] impaired microvascular functional adaptation to hypertension in the brain,[24,26] disruption of microvascular barrier function (e.g. blood brain barrier disruption[26,27]), neurovascular uncoupling,[20] activation of inflammatory processes,[28–34] impaired angiogenic capacity,[31,35,36] and alterations in the secretory function of microvascular endothelial cells.[32,37]

Studies on aged laboratory rodents, non-human primates and human subjects showed that cellular and molecular mechanisms underlying both arterial and microvascular aging include endothelial dysfunction,[38] extracellular matrix remodeling, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation and mitochondrial oxidative stress,[19,27,28,33,39–45] increased peroxynitrite production,[19,46] nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and up-regulation of pro-inflammatory cytokines and chemokines,[30,32,42,43,47,48] NF-E2-related factor 2 (Nrf2) dysfunction and impaired cellular stress resistance,[43,49,50] increased susceptibility for vascular injury,[21,23,26,27,44] mitochondrial dysregulation,[28,41] and endothelial senescence[51] and apoptosis.[30,48]

III. Potential interventions that retard cardiovascular aging

While aging was historically believed to be an inevitable and intractable process, it is now well-appreciated that aging can be modulated through various environmental, life style, genetic, and pharmacological interventions. Dietary regimens and drugs that can slow the aging process continue to raise interest among the general public as well as the scientific and medical communities.[52] There are already a few anti-aging interventions available that promote healthspan and/or lifespan extension and have been validated in at least three model organisms by three different laboratories. These interventions include fasting regimens, calorie restriction (the reduction in the intake of calories without malnutrition, CR), exercise, and the use of low-molecular-weight compounds, including metformin, resveratrol, and rapamycin.[52]

1) Cardiovascular protective effects of calorie restriction

To date, CR is the most robust intervention that has been reproducibly shown to prolong lifespan and delay the onset of age-associated diseases in both invertebrates and vertebrates, including mammals.[53,54] Therefore, the successful use of pharmacological interventions that slow aging and prevent chronic disease requires an understanding of how CR delays CV aging and increases lifespan.

There is increasing epidemiological and experimental evidence that CR confers multifaceted CV protective effects (Figure 2) in aging and in pathological conditions associated with accelerated vascular aging.[55] In laboratory animals, CR has been shown to improve endothelial function,[32,34,56,57] prevent atherosclerosis and arterial stiffening,[58] reduce myocardial interstitial fibrosis, cardiac apoptosis, and improve cardiac function.[59] CR also confers significant microvascular protection by improving endothelial angiogenic capacity, increasing cortical microvascular density,[60] and restoring microvascular NO synthesis, all of which enhancing the metabolism of parenchymal tissues.[61]

Insight into the beneficial effect of CR on several CVD and stroke risk factors in humans emanates from studies in which obese individuals were treated with some form of relatively short-term dietary restriction to lose weight. Nearly 70% of American adults are either overweight or obese, and obesity dramatically increases the risk for health problems, such as heart disease, stroke, high blood pressure (BP), type 2 diabetes and more.[1] In fact, more than 2,150 Americans die from CVD each day, claiming more lives than cancer and chronic

lower respiratory diseases combined.[1] Therefore, weight loss offers significant improvement in the incidence of CV and metabolic disease in these individuals through reduction in body mass index, body fat, total cholesterol, serum triglyceride, inflammation, and endothelial and adipocyte dysfunction.[62–64] Of significance, a diet enriched in multiple functional ingredients and concepts, i.e. natural antioxidant-rich foods, omega-3 fatty acids, prebiotics and probiotics, low-glycemic-impact foods/meals, and blood cholesterol-normalizing ingredients, reduces blood lipids and improves other cardiometabolic risk markers in healthy overweight/obese subjects in a manner that is independent of body weight reduction.[65] Moreover, results from a 6-mo clinical trial show 25% CR able to reduce the estimated 10-year CVD risk[66] in non-obese individuals, based on total and high-density lipoprotein (HDL) cholesterol (expressed as their ratio), systolic BP, age, and gender.[67] The CALERIE Study Group has recently published a 2-year study of 25% CR in non-obese individuals that shows significant decreases in body weight, serum cholesterol, triglycerides, and mean BP without adverse events.[68] The risk of coronary heart disease deaths in Asian non-obese individuals of both sexes was found to be reduced with lower energy intake.[69] While high heart rate (HR) variability is associated with improved CV function, low HR variability has been linked to poor CV function.[17,70] Long-term 30% CR (7 years on average) increases HR variability to a level comparable with published norms for healthy individuals 20 years younger, indicating a systemic effect that counters the expected age-associated changes in autonomic function.[71]

As seen in humans, studies of the effects of CR in rhesus monkeys have shown a reduction in body weight, body fat, BP, and triglyceride levels that was accompanied by improvement in glucoregulation and lipoprotein profile.[54] A 50% reduction in the incidence of CVD among CR-fed monkeys has been reported by Colman and colleagues;[72] however, this observation could not be replicated in a second CR study in monkeys,[54] probably due to differences in diet composition and feeding protocols.

Intermittent fasting is a well-established intervention that exerts beneficial effects on many biomarkers of CV aging and risk factors for CVD in humans, including a decrease in circulating C-reactive protein.[73] Intermittent fasting entails to fast on some days and feed on others, and, in doing so, reduces CV risk.[74] This CR-like regimen also improves physiological CV parameters,[75–77] facilitates weight loss, prevents the progression of type 2 diabetes, and appears to be cardioprotective by providing resistance to ischemic injury in rodents.[78,79]

Although the cellular and molecular mechanisms underlying the CV protective effects of CR regimens are still not completely understood,[55] the molecular basis of CV protection relies on its beneficial effects on the different hallmarks of aging, such as metabolism, cellular oxidative stress, inflammation, autophagy, mitochondrial activity, and stem cell function.[80] The existing evidence suggests that CR may improve vascular health by eliciting changes in circulating neuroendocrine factors.[81] In support of this concept are studies showing that circulating factors present in the sera of CR-fed rats and non-human primates confer significant anti-oxidative, anti-inflammatory and pro-angiogenic effects in cultured endothelial cells.[31,34] In addition, there is also evidence that CR activates endogenous anti-oxidative, pro-angiogenic, anti-apoptotic, and anti-inflammatory mechanisms in cell-

autonomous manner, retaining a youthful phenotype in vascular cells.[32] Previous studies suggest that sirtuins (see below) are key mediators of the anti-aging effects of CR,[82] including its anti-oxidant and anti-inflammatory vascular effects.[34] There is also important evidence that activation of Nrf2, an evolutionarily conserved transcription factor with cytoprotective and pro-survival functions, contributes to the beneficial effects of CR.[32,83] The activation of adenosine monophosphate-activated protein kinase (AMPK) by mechanistic target of rapamycin (mTOR) is another key signaling pathway implicated in CR-mediated CV protection.[84] Potentially, the aforementioned mechanisms that contribute to the effects of CR can be harnessed for the development of new pharmacological approaches to prevent and treat CV and cerebrovascular diseases in elderly patients.[85]

In response to 25–30% CR, which usually leads to a 10% decrease in body weight, and to intermittent fasting, improvement in CVD markers is observed in humans.[67,68] However, more studies are needed to understand the dynamic interplay between the degree of CR and the frequency of food consumption in the modulation of metabolic and molecular pathways and prevention of CV diseases.

2) Pleiotropic cardiovascular protective effects of GH/IGF-1 axis

Growth hormone (GH) is involved in the regulation of somatic growth and development,[86] and in the regulation of metabolism[87] by acting directly via the GH receptor and subsequent production of insulin-like growth factor 1 (IGF-1) from the liver. The local production of IGF1 in the CV system promotes paracrine signaling[88] and is associated with CV protection in humans and laboratory animals.[89–91] The systemic GH and IGF-1 levels decline progressively during aging[92] and, although controversial, GH and IGF-1 deficiency appear to be involved in the increased CVD risk and endothelial dysfunction.[93–95] The CR-mediated increase in cardiac-specific IGF-1 expression could contribute to the paracrine CV protection.[96,97] The mammalian heart has a limited amount of cardiomyocyte stem cells and this number tends to decrease with aging.[98] IGF-1 overexpression is able to prevent this loss by mounting an effective response on several fronts: delay in cellular aging and death via enhanced nuclear localization of phosphoactive protein kinase B (a.k.a. AKT) and increased telomerase activity,[99] protection against apoptosis[100] and oxidative damage, and lower replicative senescence rate of resident stem cells.[99] The use of IGF-1 as adjuvant in stem cell therapy has been demonstrated through exposure of old animals to youthful circulation –rich in circulating IGF-1 levels– by heterochronic parabiosis.[101]

It is well documented that GH deficiency and low circulating levels of IGF-1 significantly increase the risk for CV and cerebrovascular diseases in humans (for a review see reference [102]). In addition to its effect on stem cell function, significant microvascular protection is conferred by endocrine and paracrine IGF-1 signaling.[102] Microvascular dysfunction due to age-related IGF-1 deficiency has been causally linked to the pathogenesis of vascular cognitive impairment and has also implications for the pathophysiology of cardiac failure.[102] Despite evidence that treatment with low doses of GH may exert beneficial effects in the CV system, the administration of supraphysiological levels of IGF-1 is accompanied with side effects (e.g. potential diabetogenic and/or pro-tumorigenic action of IGF-1) that should be carefully monitored.

3) mTOR signaling is an important modulator of the cardiovascular aging phenotype

A leading target for anti-aging interventions is the nutrient response pathway controlled by mTOR signaling.[103,104] Inhibition of this pathway by CR extends lifespan and confers healthspan increase in various animal models.[105–109] mTOR is a serine/threonine kinase that activates cell anabolism, especially increasing protein synthesis and cell growth, while inhibiting catabolic mechanisms, notably autophagy. mTOR associates with specific adaptor proteins to form two distinct complexes, termed mTORC-1 and mTORC-2. mTORC-1 phosphorylates S6k1 or 4EBP1 to promote mRNA translation, and Akt and AMPK are the main mTORC1 regulators. Increase in nutrient and growth factors availability stimulates Akt-mediated activation of mTOR, but suppresses AMPK function. Activation of AMPK occurs during stress or energy deprivation, thereby inhibiting mTOR.[103,110] The fundamental role of mTOR signaling in metabolic regulation contributes to the biogenesis and proper functioning of the CV system.[111] In fact, embryos lacking mTORC1 or mTORC2 have failed to develop.[112] Genetic disruption of mTORC1 in mouse myocardium has been implicated in dilated cardiomyopathy, through activation of autophagy and apoptosis, and accumulation of 4EBP1 associated with an increase in heart failure.[113] Mice deficient in raptor (component of the mTORC1 complex) had impaired metabolism at first, followed by high mortality a few weeks later due to dilated cardiomyopathy caused by increase in autophagy and apoptosis, and reduction in cardiomyocyte growth.[114] Similarly, deletion of Rictor (mTORC2 complex member) is lethal for most embryos, but the surviving mice display CV abnormalities.[115] However, a down-modulation of mTOR signaling confers CV benefits in the aging animals as evidenced by the fact that the mTORC-1 inhibitor rapamycin has been reported to attenuate load-induced cardiac hypertrophy, dampen the increase in myocyte cell size,[116,117] and reduce ischemic injury after myocardial infarction.[118,119] Furthermore, female mice supplemented with rapamycin late in life showed improved CV aging through the decrease in inflammation and hypertrophy, and higher metabolism.[120]

There is a progressive incidence of cardiac hypertrophy and diastolic dysfunction with advancing age as well as accumulation of protein damage mediated by oxidation and ubiquitination. Of significance, these age-associated conditions are hampered by short term CR and rapamycin treatment.[104] Inhibition of mTORC1 by rapamycin confers protection against these age-related CVD, especially in the presence of metabolic disorders. In fact, mTOR appears to be dysregulated with aging, and, therefore, a partial inhibition of this pathway allows for better control of mTOR activity in CV aging.[111] By acting as a regulator of cell growth and proliferation, mTOR is also responsible for stem cell exhaustion and dysfunction. So, mTOR inhibition is beneficial also for the preservation of cardiac stem cell pool that normally decreases during aging and disease.[121]

4) Sirtuin activation confers diverse anti-aging cardiovascular protective effects

Members of the sirtuin family of protein deacetylases are among the best-studied mediators of CR, and the contribution of SIRT1 (silent information regulator 1, after the yeast Sir2) has been the most extensively examined. The NAD^+-dependent deacetylase SIRT1 is involved in several key cellular functions, including chromatin remodeling - through histone deacetylation – and gene expression, and also in cellular energy metabolism.[122] The deletion

of SIRT1 interferes with CR-mediated lifespan extension in yeast, worms and flies.[123_125] There is strong evidence that SIRT1 exerts multifaceted anti-atherogenic,[126] anti-inflammatory,[127] endothelial protective,[128] and cardioprotective[129] effects. These findings have led to the search of small molecule activators of SIRT1 as therapeutics to improve CV health. Earlier studies have established that the natural polyphenol resveratrol was able to activate Sir2 in yeast and SIRT1 in humans, and increasing cell survival through acetylation of p53.[130] In rodents, resveratrol promotes transcriptional responses comparable to CR-mediated SIRT1 activation,[130] improves health and survival of mice on a high-calorie diet,[131] and confers multifaceted anti-aging vascular effects (including potent mitochondrial protective and anti-inflammatory effects) and protection against atherosclerosis, hypertension, ischemia/reperfusion injury, and heart failure.[20,43,132_139] Resveratrol improves cerebromicrovascular function,[20] increases cerebromicrovascular density[140] and prevents cerebral microhemorrhages,[141] all of which likely contribute to resveratrol-mediated improvement of cognitive function in aged mice.[140] Pre-clinical studies also indicate that resveratrol supplementation reduces platelet aggregation[142] and improves lipid metabolism,[143] while inhibiting atherosclerotic plaque formation[144] and markers of oxidative stress and inflammation.[145,146] It is within this context that resveratrol improves arterial stiffness in non-human primates fed high-fat, high sugar diet through decreased levels of caspase 3 and lipid peroxidation.[147] However, resveratrol also elicits off-target cellular effects, whereby AMPK is activated in a SIRT1-independent fashion[148_150] and phosphodiesterases inhibited nonselectively, causing a rise in intracellular cAMP levels with concomitant, sirtuin activation and improvement in age-related phenotypes.[151] The redox-sensitive transcription factor Nrf2 is potently activated by resveratrol.[43,135,137] The limited number of randomized clinical trials has generated controversial results on the effect of resveratrol supplementation in humans. It would appear that resveratrol is associated with lower CVD marker levels and reduced obesity at least when studies were conducted in subjects with metabolic syndrome (reviewed in [152]). SRT1720 is a specific, synthetic SIRT1 activator that has demonstrated health and lifespan benefits in models of accelerated aging.[153,154] There is improvement in endothelial function and attenuation in vascular oxidative stress and inflammation in SRT1720-treated mice as they age.[155] SRT1720 possesses also anti-atherogenic activity.[156] The polyphenol S17834, which up-regulates SIRT1, has similar anti-inflammatory and anti-atherogenic actions and exerts cardioprotection in mice with accelerated CV aging phenotypes.[157_159]

There are several other natural polyphenols with antioxidant, anti-inflammatory, anti-apoptotic and/or anti-senescence properties, including quercetin, kaempferol and epicatechin, which may also potentially exert beneficial effects in CV aging either alone or in combination with existing drugs. However, rigorous pre-clinical and clinical studies are needed.

5) Cardiovascular protective effects of PARP-1 inhibitors in aging

Pharmacological inhibition of the PARP pathway has emerged as a potentially important therapeutic target for aging and age-associated diseases.[16,160] PARP-1 is a member of the DNA damage surveillance network. The catalytic activity of PARP-1 was reported to increase in old age due to the age-related increases in peroxynitrite-mediated DNA strand

interruptions.[161_163] Upon activation PARP-1 ADP-ribosylates various nuclear proteins, including transcription factors and histones, and, as a consequence, it regulates a range of cellular pathways at the transcriptional level.[164,165] PARP-1 activation up-regulates NF-κB-dependent inflammatory gene expression, which is highly relevant in CV aging.[166_168] PARP-1 is a NAD^+-consuming enzyme that competes with SIRT1 for the same pool of NAD^+. An increase in PARP-1 activity results in SIRT1 inhibition due to lower substrate availability.[169] This antagonistic crosstalk between PARP-1 and SIRT1 represents a potentially important mechanism by which PARP-1 over-activation promotes age-related cardiac and vascular dysfunction. Indeed, there is evidence suggesting that inhibition of PARP-1 may confer protection against CV aging.[16,46,160,163,170]

6) Activation of AMPK pathway in cardiovascular aging

Studies in invertebrates have indicated in link between increase in AMPK activity and lifespan extension.[171] However, the role of AMPK in the health-protective effects of CR in mammals is under debate. AMPK has been traditionally viewed as an intracellular energy switch, but is now described as a key player in maintaining physiological processes in both the heart and the vasculature.[172] Expression of constitutively active AMPK mutations produces extensive remodeling of the metabolic network in order to maintain energetic homeostasis[173] at the expense of developing glycogen-storage cardiomyopathy.[174] A number of cellular processes that either decrease ATP levels or increase AMP concentrations promote activation of mammalian AMPK. Moreover, pharmacological interventions that include metformin, aspirin, 5-aminoimidazole-4-carboxamide riboside, statins, thiazolidinediones and the phytochemicals berberine, quercetin, and resveratrol have the ability to activate AMPK signaling[175,176] by rising the (AMP+ADP)/ATP ratio as a consequence of mitochondrial electron transport and/or glycolysis inhibition. Notably, the anti-diabetic drug metformin provides protection against the development of hyperglycaemia-induced vascular disease through improvement in endothelial function.[177] This biguanide exerts vasoprotection via activation of AMPK[178] even though some cellular actions could be mediated in an AMPK-independent pathway.[179] Resveratrol lowers BP in spontaneously hypertensive rats and reduces cardiac hypertrophy through AMPK signaling.[180,181] Aspirin, also known as acetylsalicylic acid, is used at low doses as an antiplatelet drug in the prevention of vascular ischemic events and has been shown to increase lifespan in genetically heterogeneous male mice.[182] This nonsteroidal anti-inflammatory drug activates AMPK[183] to decrease the expression of inducible nitric oxide synthase (iNOS) and Cox-2[184] and, therefore, lowers inflammation and oxidative stress. Similar protective effects have been observed with berberine.[184] These results have shed light on how metformin, aspirin, and other compounds promote lifespan extension.[185_187]

7) Anti-aging effects of interventions that reduce oxidative stress and improve NO bioavailability

NO is a crucial factor for the health and function of the aged CV system. One of the consequences of increased oxidative stress in aging is a functional inactivation of NO,[19,188_190] resulting in significant vasomotor dysfunction and contributing to vascular inflammation, atherogenesis, and cellular energetic imbalance.[42] Studies on genetically NO-deficient mice have linked the impaired NO bioavailability with increased mortality and

reduced lifespan potential.[15,191,192] Several experimental anti-aging interventions exist (e.g., CR,[32,34,61,128,193] SIRT1 activators, resveratrol,[20,43,48,137–139] rapamycin,[194] TNFα antibodies,[40] and treatment with NADPH oxidase inhibitors or antioxidant compounds[195]) that improve NO bioavailability by means of increased production and/or lower NO degradation caused by oxidative stress.

The antidiabetic drug metformin has been shown to have favorable haemodynamic and rheological effects in elderly patients with CV risk factors. Infusion of the endothelial NOS (eNOS) substrate L-arginine enhances the hemodynamic effects of metformin in type 2 diabetic patients[196] through increased blood flow in muscle and adipose tissue, reduction in systolic BP in response to vasoconstrictors, and improvement in acetylcholine-mediated vasodilation.[197–199] Although activation of AMPK partly mediates the pleiotropic effects of metformin, studies have shown that the biguanide improves NO-mediated endothelial-dependent vasodilatation under insulin-resistant conditions[177] by mechanisms linked to increased phosphorylation of eNOS and Akt via SIRT1- and AMPK-independent pathways.[200] However, the ability of metformin to regulate endothelial progenitor cell differentiation[201] and stimulate ischemia-induced revascularization[202] depends on AMPK/eNOS signaling cascade. Metformin also has vascular anti-inflammatory properties by down-regulating NF-κB activation, caused by phosphorylation of its inhibitor IκB in the vessel wall of experimental atherogenesis in rabbits, and decreasing serum levels of high-sensitivity C-reactive protein.[203]

The most commonly used classes of drugs to treat obese patients have pleiotropic antioxidant properties that contribute to their beneficial effects. Studies show that statins reduce reactive oxygen species (ROS) production in cardiac muscle, which leads to an increase in mitochondrial biogenesis and phase II antioxidant enzyme system via the PGC-1 signaling pathway.[204] In endothelial cells, the activation of AKT by statins results in stimulation of eNOS activity, leading to increased NO synthesis and neoangiogenesis while the increased production of endothelial NO in the central nervous system points to a role for statins in regulating sympathetic and vagal outflow, and inhibiting central angiotensin-II mechanisms.[205] Clinical trial results show that statin use has been associated with lower mortality in elderly people from age 85 to 90 by providing total cholesterol-independent benefits.[206]

8) Anti-aging effects of mitochondria-targeted antioxidants

There is strong evidence that with advanced age mitochondrial production of ROS significantly increases in the heart[207] and vasculature.[208] Direct evidence supporting a critical role of mitochondrial ROS in cardiac aging was demonstrated by studies in mice that overexpress catalase targeted to the mitochondria. These mice show 18% extension of lifespan associated with protection against cardiac aging phenotypes.[209,210] These observations have led to the development and testing of mitochondria-targeted antioxidants, including Mito-Q, MitoTEMPO, mitovitamin E, mitophenyltertbutyline, and SkQ1, for their potential anti-aging CV protective effects. The Szeto-Schiller (SS) compounds represent a novel class of potent mitochondria-targeted antioxidants capable of preserving mitochondrial function by scavenging H_2O_2, hydroxyl radical, and peroxynitrite.[211,212] The tetrapeptide

SS-31 has been shown to reduce ischemia reperfusion injury and reperfusion arrhythmia and better preserve myocardial function in various infarct models.[213,214] Although studies on aged Apoe$^{-/-}$ mice show that treatment with MitoTEMPO exerts anti-atherogenic effects,[215] further research is needed to test the therapeutical benefits of mitochondria-targeted antioxidants on a range of age-related CV and cerebrovascular phenotypes both in animal models of aging and elderly humans.

9) Anti-aging effects of polyunsaturated fatty acids

There are two dietary classes of essential PUFAs, the n=6 PUFAs found primarily in vegetable oils and n=3 PUFAs mainly present in marine animals or plants. Commonly referred to as omega-3 fish oils or omega-3 fatty acids, n=3 PUFAs have been shown to be beneficial in CVD as a secondary prevention and are commonly used to lower high triglyceride levels in the blood. Experimental evidences have revealed multiple underlying molecular mechanisms of action for omega-3s, which include membrane modification, ion channel attenuation, regulation of pro-inflammatory gene expression, and production of lipid mediators.[216] However, the mechanism(s) that contributes the most to the cardioprotective effects of PUFAs remains to be clarified. It is imperative that further testing be performed regarding the use of omega-3 supplementation (above the accepted minimum requirement) as a mean to slow aging and reduce diseases. Indeed, pre-clinical studies have shown that long-term intake of fish oil decreases lifespan in senescence-accelerated mice[217], long-lived F1 mice[218] and *C. elegans*.[219]

10) Anti-aging effects of Nrf2 activators

The redox-sensitive transcription factor Nrf2 plays an evolutionarily conserved role in orchestrating cellular antioxidant defenses and maintaining redox homeostasis, ultimately impacting on health span and/or lifespan.[83,220_224] Recent evidence suggests that Nrf2 also regulates the proteasome and removal of oxidized proteins.[225] Nrf2 has a critical role in preserving a youthful CV phenotype and maintaining the functional integrity of the heart and the vasculature.[36,226] Accumulating evidence suggests that an age-related decline in cellular Nrf2 activity results in increased cellular sensitivity to the harmful effects of ROS in the aged CV system.[49,50,55] Age-associated impairment of homeostatic responses that depends on Nrf2 has been linked to exacerbation of vascular oxidative stress[49,50] and inflammation,[43,227] impairment of angiogenesis,[36] and increased atherogenesis.[226] Importantly, activation of Nrf2 is thought to contribute significantly to the beneficial effects of CR,[32,83] rendering Nrf2 an attractive drug target for anti-aging interventions. Accordingly, an increasing number of experimental and clinical studies focus on the beneficial effects of compounds that activate Nrf2, such as sulforaphane, found in broccoli, and isoflavones, in animal models of age-related CV and cerebrovascular diseases.[228,229] The CR-mimetic resveratrol is also a potent activator of Nrf2,[43,135,137] suggesting that Nrf2 activation may also contribute to the potent anti-aging vasoprotective effects of this polyphenol.[20,230]

11) Disruption of angiotensin II signaling offers anti-aging effects

Angiotensin converting enzyme (ACE) inhibitors and nonpeptide blockers of angiotensin II type 1 receptor (AT1) are currently used widely to treat hypertension and cardiac heart

failure. The ACE inhibitor, enalapril, does not improve longevity in healthy mice,[231,232] despite the increase in heart mitochondria number and decrease in myocardial sclerosis.[232] Enalapril increases rat lifespan[233] and promotes NO production through activation of mitochondrial NOS activity.[234] Ramipril, another ACE inhibitor, doubles the lifespan of hypertensive rats by improving cardiac function and metabolism as well as enhancing eNOS-mediated increase in endothelial function.[235] Impairment in NO-dependent endothelial function in patients with Type II diabetes is aggravated by dyslipidemia and hypertension, which can be restored by ACE inhibition and weight loss.[236] The generation of pro-oxidant molecules in response to angiotensin II contributes to cell oxidation and tissue damage both in normal aging and in CV and metabolic diseases.[237] As predicted, targeted disruption of the Agtr1a gene that encodes AT1A has led to a marked increase of lifespan in mice.[238] Long-term pharmacological inhibition of AT1 with fonsartan results in the doubling of lifespan in hypertensive rats, together with improvement in cardiac function and metabolism, and enhanced endothelial function.[239] The clinical benefits of AT1 blockers can be explained by the increase in eNOS expression in the heart and carotid artery, and marked reduction in tissue ACE expression/activities.[239]

Non-selective beta-adrenergic blockers, widely used to treat hypertension and ischemic heart disease, have been proposed as anti-aging drugs. Metoprolol and nebivolol increase mean and maximal lifespan in flies and median lifespan in mice[240] and celiprolol prevents the transition to heart failure via NO-dependent mechanisms in mice.[241]

The incidence of heart failure increases progressively with advanced aging. There are many treatment modalities available for heart failure associated with reduced contractile function of the myocardium. In addition to vasodilators and diuretics, which relieve cardiac workload, therapeutic approaches for heart failure include inotropic agents that increase cardiac contractility by working either through increasing the influx of calcium or modulating adrenoreceptor signaling in cardiac myocytes. Myofilament calcium sensitizers (such as omecamtiv mecarbil)[242–244] represent a new class of inotropic agents that may be used in the treatment of heart failure. Omecamtiv mecarbil facilitates actin-myosin cross bridge formation, increases the number of myosin heads involved into the force generation, and stimulates myosin ATPase activity, which result in prolonged systolic ejection time and increased ejection fraction. The apparently disparate effects of omecamtiv mecarbil on myocardial oxygen consumption in animal models warrants further studies.[243,245] Other emerging new treatments capable of restoring systolic function include the potentiation of cardiomyocyte contractility, increase in cardiomyocyte survival and adaptive hypertrophy, and promoting vascularization (for an excellent overview see reference[246]).

The lack of effective treatment options for patients with heart failure associated with age-related diastolic dysfunction is a growing clinical problem.[247] To design effective therapeutic interventions it is important to understand the various age-related pathophysiological factors contributing to diastolic stiffness. Our current understanding is that age-related diastolic stiffness is due to cardiac remodeling, cardiomyocyte hypertrophy, interstitial fibrosis with increased deposition of collagen and other extracellular matrix components, decreased elastin content, matrix metalloprotease activation, redox imbalance and increased inflammation and/or impairment in active diastolic relaxation.[247]

Phosphorylation of the myocardial protein titin is also an important molecular determinant of cardiomyocyte stiffness,[248,249] which can be potentially modulated by therapeutic interventions.[250]

12) Progeria and cellular senescence in cardiovascular aging

The dynamic organization of the cell nucleus is profoundly modified during growth, development and senescence. Three different diseases of accelerated aging have been associated with defects of the nuclear lamina, including Hutchinson–Gilford progeria syndrome (HGPS), Mandibuloacral Dysplasia (MADA and MADB) and atypical-Werner syndrome.[251] Treatment with the mTOR inhibitor rapamycin favors recruitment of p53-binding protein 1 or 53BP1, a key player in the DNA-damage response, to the nuclear envelope and affects the levels of prelamin A in a pattern reminiscent of that observed in cells from centenarians.[252] The link between mTOR pathway and nuclear lamina defects deserves further study.

Cell senescence has been proposed to have a role in CV aging because cells positive for the cyclin-dependent kinase inhibitor p16Ink4a are key drivers of an age-related cardiac phenotype that leads to lifespan shortening in mice.[253] In patients with their first acute myocardial infarction, tight glycemic control reduces senescent myocyte precursor cells, thus increasing the regenerative potential of the ischemic myocardium.[254] Moreover, the secretory phenotype of p16Ink4a–positive cells includes many pro-inflammatory cytokines and chemokines and matrix metalloproteinases (MMP), which are involved in tissue remodeling. It is known that MMP-9 increases with age and its deletion in aged mice alleviates cardiac fibrosis and preserves LV diastolic function by modifying the extracellular matrix response and angiogenesis.[255,256] Some drugs reduce MMP-9 expression such as atorvastatin,[257] *Rosa hybrida* extracts[258] or memantine.[259] Also, inhibition of chymase, an angiotensin II-forming enzyme that activates MMP-9, has been proposed as a potentially target to prevent CV diseases.[260] Therefore, the therapeutic removal of senescent cells and reduction of MMP and chymase activities may be an attractive approach to improve CV aging and extend healthy lifespan.

IV. Perspectives

Although significant progress has been achieved in describing age-related alterations in cardiac and vascular function and phenotypes, the specific roles for cell-autonomous and non-cell-autonomous mechanisms involved in CV aging processes need to be elucidated further. It is critical to understand the interactions of age-related molecular mechanisms in vascular cells with both CVD pathogenesis and systemic aging processes, and to develop interventions targeting these mechanisms to retard CV aging. Several examples of such potential therapies include CR mimetics, mitochondrial protective agents and mTOR inhibitors. There is reasonable consensus that oxidative stress and inflammation play a critical role in the pathogenesis of a range of age-related CV and cerebrovascular diseases. The concept that the same evolutionarily conserved pathways (such as sirtuins and Nrf2) controlling the aging process in mammals also determine CV health through changes in ROS production, cellular and organismal sensitivity to oxidative stress and inflammatory

processes, raises the question of whether pharmacological or nutritional modulation of these pathways is effective both in retarding aging and delaying the onset of age-related CVD. Compelling evidence for circulating factors that alter aging phenotypes comes from studies using heterochronic parabiosis (e.g. reversal of age-related cerebromicrovascular rarefaction[261]). Further understanding of the circulating factors responsible for the transposition of the aging phenotypes in young mice and the induction of youthful phenotypes in aged mice in heterochronic parabiotic pairs will guide future experimental and translational studies on novel therapeutics to treat age-related CVD and to improve healthy CV aging. Significant advances have been made in recent years toward understanding the association between cellular senescence, aging, and age-related pathologies. Studies in genetically modified mice that express a drug-activated suicide gene specifically in senescent cells suggest that senescent cell clearance can ameliorate age-related organ dysfunction.[262] These findings led to the recent development of small molecule senolytic agents to decrease senescent cell burden in aging.[262,263] Research efforts should also persist in these directions to fully elucidate the specific relationship between cellular senescence in development of age-related CVD and, ultimately, to determine whether senolytic agents can reduce CV morbidity and mortality in the elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

ACE	angiotensin converting enzyme
AKT	protein kinase B
AMPK	adenosine monophosphate-activated protein kinase
AT1	angiotensin II nonpeptide type 1 receptor
BP	blood pressure
CR	calorie restriction
CV	cardiovascular
CVD	cardiovascular diseases

eNOS	endothelial nitric oxide synthase
GH	growth hormone
HR	heart rate
IGF-1	insulin-like growth factor 1
iNOS	inducible nitric oxide synthase
MMP	metalloproteinase
mRNA	messenger RNA
mTOR	mechanistic target of rapamycin
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
NOS	nitric oxide synthase
Nrf2	NF-E2-related factor 2
PARP-1	poly(ADP-ribose) polymerase 1
PUFA	polyunsaturated fatty acid
ROS	reactive oxygen species
SIRT1	silent information regulator 1
SS	Szeto-Schiller

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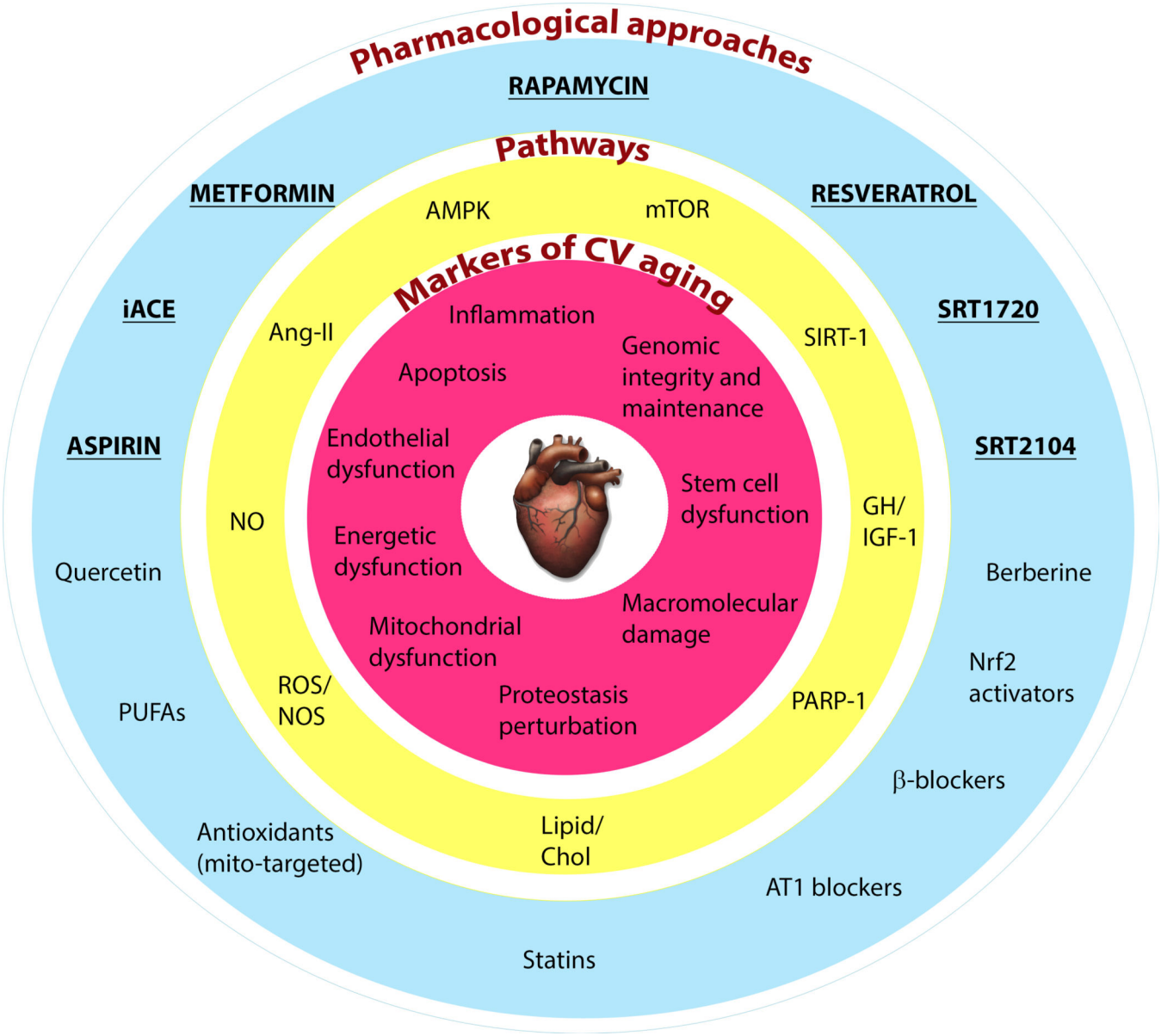

FIGURE 1. Pharmacological strategies to combat cardiovascular aging

Age-associated changes in cardiac and vascular properties (depicted in the inner red circle) can be delayed by targeting the related pathways (in the middle yellow circle) with small molecules (represented in the outer blue circle). Some of the pharmacological strategies highlighted in the diagram (bold and underlined) have been shown to improve longevity in healthy mammals. AMPK, 5' adenosine monophosphate-activated protein kinase; Ang-II, angiotensin II; AT1, angiotensin II receptor, type 1; Chol, cholesterol; GH, growth hormone; iACE, inhibitors of angiotensin-converting enzyme; IGF-1, insulin-like growth factor-1; mTOR, mechanistic target of rapamycin; NO, nitric oxide; NOS, nitric oxide synthase; Nrf2, NF-E2-related factor 2; PARP-1, poly (ADP-ribose) polymerase 1; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SIRT-1, sirtuin (silent mating type information regulation 2 homolog) 1.

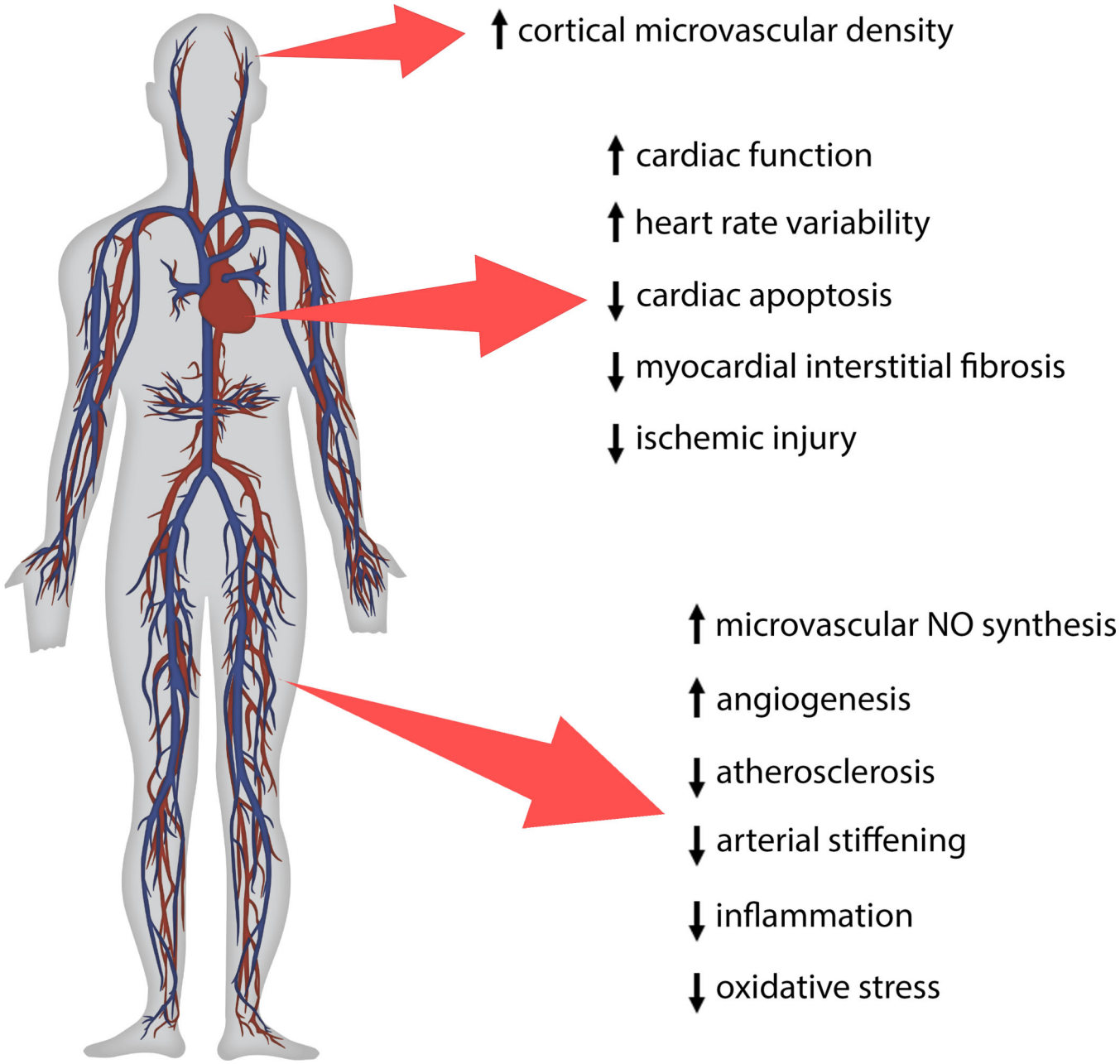

FIGURE 2. Anti-aging effects of caloric restriction in the cardiovascular system

The up-arrow notation indicates an improvement or increase while the down-arrow shows decrease or impairment of cardiovascular functions and pathologies. NO, nitric oxide.

Table 1

List of terms and their definitions

List of terms	Definitions
Cause of death	The disease or injury, which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury
Healthspan	Period of time of disease-free health
Lifespan	Amount of time that a person or animal actually lives
Morbidity	Incidence or prevalence of a disease or of all diseases
Mortality rate	Measure of the number of deaths in a given population

Table 2
Pharmacological strategies to retard cardiovascular aging

Mechanism of action of various interventions and their effects on lifespan extension, if any, and on the CV system are described.

Intervention or compound	Main mechanism of action	Lifespan extension	Effects on the CV system
Calorie Restriction	• Sirt1 activator • AMPK activator • mTOR inhibition • NRF2 activator?	• Yeast, flies, worms, mice • Healthspan and possibly average life span in primates and humans.	• Reduction of body weight, body fat and blood pressure, increase in insulin sensitivity, improved lipid profile and adipocyte dysfunction, and improvement of endothelial function[32,34,56,57] • Prevention of atherosclerosis and arterial stiffening[58] • Reduction of myocardial interstitial fibrosis, cardiac apoptosis, and improvement of cardiac function[59] • Confers microvascular protection by improving endothelial angiogenic capacity and increasing cortical microvascular density[60] • Restoring microvascular NO synthesis, enhancement of metabolism of parenchymal tissues[61]
Rapamycin	• mTOR inhibitor	• Yeast, flies, worms, mice	• Attenuation of load-induced cardiac hypertrophy, restraint in the increase in myocyte cell size[116,117] • Reduction of ischemic injury after myocardial infarction[118,119] • Decrease in inflammation and hypertrophy[120] • Higher metabolism[120] • Preservation of cardiac stem cell pool[121]
Metformin	• Increase in AMPK activity	• Yeast, flies, worms, mice • Diabetic humans (under clinical trials)	• Improvement in endothelial function[178] • Increase in blood flow, reduction in systolic BP

Intervention or compound	Main mechanism of action	Lifespan extension	Effects on the CV system
			and improvement in vasodilation[198_200] • Regulation of endothelial progenitor cell differentiation[202] • Stimulation of ischemia-induced revascularization[203] • Improvement in vascular anti-inflammatory properties and decrease of serum levels of high-sensitivity C-reactive protein[204]
Resveratrol	• Sirt1 activator • AMPK activator?	• Yeast, worms • Controversial results in flies, mice and humans	• Lowering of blood pressure, increase in flow-mediated dilatation of the brachial artery, improvement of endothelial function, decrease in plasma inflammatory biomarkers (in humans, depending on the metabolic state of patients)[152]
SRT1720/ SRT2104	• Sirt1 activators	• Mice and rats • Under clinical trial for humans	• Improvement in endothelial function and attenuation in vascular oxidative stress and inflammation[155] • Anti-atherogenic activity[156]
ACE inhibitors	• Angiotensin- converting enzyme inhibition	• Worms and rats	• Increase of NO production[234] • Improvement in cardiac function and metabolism and endothelial function[235]
Aspirin	• Irreversible inactivation of cyclooxygenases • AMPK activator	• Male mice	• Decreased expression of inducible nitric oxide synthase (iNOS) and Cox-2 [184]
Statins	• Inhibition of HMG-CoA reductase	• Flies	• Reduction in ROS levels in cardiac muscle[204] • Increased NO synthesis and neoangiogenesis in endothelial cells and the central nervous system[205]

Intervention or compound	Main mechanism of action	Lifespan extension	Effects on the CV system
β-Blockers	• β-adrenergic receptor antagonists	• Flies • Only mean lifespan in mice	• Use in treatment of hypertension and ischemic heart disease, prevention of the transition to heart failure via NO-dependent mechanisms (celiprolol)[241]
AT1 blockers	• Angiotensin II receptor antagonists	• Hypertensive mammals	• Improvement in cardiac function and metabolism, and enhanced endothelial function[239] • Increase in eNOS expression in the heart and carotid artery, and marked reduction in tissue ACE expression/ activities[239]
Omecamtiv mecarbil	• Enhances myosin and actin cross-bridge formation	• Unknown	• Prolonged systolic ejection time and increased ejection fraction • Disparate effects on myocardial oxygen consumption
Berberine	• AMPK activator	• Flies	• Decrease in the expression of iNOS and Cox-2 as well as increase the (AMP +ADP)/ATP ratio by impeding the efficiency of mitochondrial electron transport[176]
PUFAs	• Peroxidation • Membrane modification • Formation of lipid mediators	• Low amounts increase lifespan in worms • High amounts decrease lifespan in worms and mice	• Lowering of triglyceride levels in the blood[216]
Nrf2 (*Nfe2l2*) activators	• Activate NRF2- antioxidant response	• Flies and worms	• Regulation of cellular antioxidant defenses and maintenance of redox homeostasis[83,220–224] • Regulation of the proteasome and removal of oxidized proteins[225] • Maintenance of the functional integrity of the heart and vasculature[36,226]
Mito-targeted antioxidants	• Anti-oxidant	• Controversial results	• Reduction of ischemia reperfusion injury and reperfusion arrhythmia

Intervention or compound	Main mechanism of action	Lifespan extension	Effects on the CV system
		• Sex-specific effects in flies and rodents	and preservation of myocardial function[213,214] • Anti-atherogenic effects[215]