
Biology of Aging and Implications for Heart Failure Therapy and Prevention

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Introduction

The elderly population (age ≥ 65 years) with heart failure (HF) has been increasing significantly in developed countries since the early 1970s and is currently increasing in most developing countries. The projections from population studies in the United States (USA), Europe, and other developed countries suggest that the worldwide trend in the growing burden of HF will very likely continue and tax healthcare systems worldwide [1, 2]. In the USA, the number of elderly people is expected to double by 2030 [1], and the very old aged ≥ 85 years will likely triple by 2050 [2]. While improvements in public health, nutrition, medical therapies, and healthcare delivery systems have undoubtedly contributed to growth of the elderly population, there has been a concurrent even steeper growth of the elderly with HF in the USA and Europe [3–5]. Data from the National Health and Nutrition Examination Survey (NHANES) in the 2010 Heart Disease

and Stroke Update of the American Heart Association (AHA) have clearly shown that the increase in HF prevalence is age dependent and the prevalence highest in elderly men and women [4]. Similar trends as in the USA [5] were found in Canada [6, 7]. Unless appropriate preventive strategies and measures are implemented urgently, the prevalence, related complications, and total burden of HF in elderly men and women will very likely expand and tax the future healthcare systems even more.

Many authors since the 1990s have commented on the increasing economic burden due to mortality, morbidity, hospitalization, and emergency department visits in the growing adult and elderly populations with HF [5–14]. Prevention of HF in the present and future elderly populations should therefore be a healthcare priority. However, when, where, and how to begin needs to be clearly defined [15]. Because aging is a progressive biological process, objective management and prevention of HF should consider the pathobiology of aging and the pathophysiological changes associated with cardiovascular (CV) aging in the context of the aging-HF continuum [11, 15] and the possible need for different treatment strategies for different age groups [9, 15]. Furthermore, preventive measures should logically begin early, in younger age groups, from the pediatric age through early and late adulthood for maximal effectiveness in combating the rising burden of HF [15]. This chapter addresses these points and suggests some potential preventive strategies for achieving optimal impact.

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Aging, the Elderly, and Cardiovascular Disease

There are several definitions of aging in humans, including chronological, biological, physiological, and clinical (Table 2.1). Despite advances in the biology of aging, the chronological age of 65 years is still the accepted age cutoff for the elderly in most developed countries, although it has been shown to have considerable relevance in population studies and clinical trials [9]. Population and epidemiological studies have established that the population of elderly people aged ≥ 65 years is not only increasing worldwide but the elderly group has the greatest burden of HF and the highest morbidity and mortality from CV disease (CVD) and other comorbidities [4, 16–18]. These studies also show that increasing chronological age is associated with increased CVD risk, including that for hypertension, coronary heart disease (CHD), stroke, and HF [4]. Importantly, this aging-related growth in healthcare burden has resulted in concurrent increase in healthcare costs [4], thereby providing strong justification for more research to address how aging might lead to CVD and HF.

Biology of Aging and Risk of Cardiovascular Disease

Cumulative evidence indicates that aging is an inevitable, natural biological process that progresses with the passage of time. The aging process may therefore result in important biological differences between young, adult, and old patients that may differentially impact pathophysiology and optimal management of HF [19–21]. For example, aging is associated with biological and CV changes that impact disease expression and response to therapy [19–21]. As mentioned above, aging also results in increased CVD risk, including hypertension and CHD [4] which lead to HF [10, 19–21]. Recent studies suggest that aging is associated with defective responses to myocardial injury and impaired wound healing, leading to adverse LV remodeling and HF [10, 19–21].

Table 2.1 Definitions of aging

Type	Basis
Chronological	Socioeconomic and political
Biological	Telomere length, telomere activity
Physiological	Aging phenotype
Clinical	Biomarker

Table 2.2 Aging phenotype and heart failure

Increased LV concentric remodeling
Increased LV mass to volume ratio
Increased extracellular matrix, fibrillar collagen content, fibrosis
Impaired LV diastolic function and relaxation
Heart failure-preserved ejection fraction
LV left ventricular

At the cellular level, aging is genetically driven and characterized by progressive decline in the capacity of cells to divide and carry out their specific functions [19]. Several markers correlate with the aging phenotype (Table 2.2). As discussed below, telomeres, which are DNA sequences at the end of chromosomes, shorten with every cell division and therefore with aging. On the other hand, telomerase, the cellular enzyme that adds telomeric repeat sequences to chromosomal ends, preserves telomere length. Telomerase may also decrease with aging under certain conditions. Low telomerase activity and short telomere lengths may be early markers of CV risk. In the West of Scotland Coronary Prevention Study (WOSCOPS), where patients aged 45–65 years were randomized to placebo or pravastatin, shorter leukocyte telomere length predicted CHD in middle-aged men. Importantly, for every 10 years increase in age, telomere length decreased by 9 % [22]. In a recent nested case-control study, shorter telomere length was related to risk of myocardial infarction [23].

Pathophysiologic Correlations and Remodeling During Aging

At the clinico-pathophysiological level, several biological changes that occur with aging contribute to adverse cardiac remodeling and the relentless march to HF [19, 20]. We previously

Table 2.3 Heart failure and changes in cardiovascular physiology and pathophysiology with aging

• Vascular remodeling
– ↑ Ventricular-arterial stiffening and altered coupling
– ↑ Systolic blood pressure and pulse pressure
• Ventricular remodeling and ↑ mass/volume ratio
– ↑ Extracellular matrix (fibrillar collagen) and ↑ fibrosis
– ↑ Advanced glycation end products (AGES)
– ↑ Collagen cross-linking
– Diastolic dysfunction and impaired relaxation
– ↓ Cardiac reserve
• Atrial remodeling and atrial fibrillation
– Cellular and subcellular remodeling
– Altered responses to stress
– Altered responses to injury and impaired healing
• CV remodeling due to lifelong exposure to CV risk factors
– ↑ Interaction with CV risk factors
– ↑ Risk of coronary heart disease and sequelae
– ↑ Risk of peripheral artery disease and sequelae
– ↑ Risk of cerebrovascular disease and sequelae
– ↑ Risk of comorbidities and sequelae
– ↑ Cardiorenal interactions and sequelae
– ↑ CV events

↑, increase; ↓, decrease; CV cardiovascular

Table 2.4 Heart failure and changes in cardiovascular biology and pathobiology with aging

• ↓ Leukocyte and tissue telomere length
• Altered gene regulation
• Altered cellular and subcellular functions
• Altered mitochondrial population and function
• ↓ Myocyte number, ↑ myocyte size
• Altered contractile pathways, ↓ myocardial contractility
• Isomyosin shift
• ↓ Excitation–contraction coupling
• ↑ Fibrosis-related genes, ↑ fibrosis and collagen matrix
• ↑ Myocardial stiffness, ↑ vascular remodeling and stiffness
• ↑ End-systolic stiffness (chamber elastance)
• ↓ Diastolic compliance
• Altered immune responses, altered repair responses
• Altered responses to injury, impaired healing
• Remodeling of beta-adrenergic system
• Altered neurohumoral pathways
• ↑ Angiotensins and endothelins, ↑ angiotensin II
• Altered stress response pathways
• ↑ Oxygen-free radicals, ↑ oxidative stress and damage
• Altered cardiac and arterial responses to stress
• Altered metabolism and metabolic reserve

↑, increase; ↓, decrease

hypothesized that aging is associated with global remodeling that involves changes in CV structure as well as cellular, subcellular, biochemical, molecular, physiological, and pathophysiological pathways and responses [19–21]. As a corollary, the collective aging-related biological and CV changes may impact both disease expression and response to therapy and have important therapeutic implications for HF management. Importantly, several biological changes contribute to adverse cardiac remodeling and the march to HF during aging [15, 19]. Since the aging process is progressive, it follows that HF management must consider the aging-dependent pathophysiological changes (Tables 2.3 and 2.4) and possibly the need for different treatments for different age groups in order to maximize benefits. Therapy of CVD that is optimal for the young patient may therefore not be optimal for the old patient. This also applies to HF.

Expanding knowledge of the biology of aging [8–11] and aging-related changes in CV structure and function [24–27] suggest that the aging heart may itself be a substrate for CVD including HF. In the last three decades, a constellation of typical aging-related physiological and pathophysiological changes typical in the CV system (Table 2.3) and pathobiological changes (Table 2.4) as well as an aging phenotype (Table 2.2) have been recognized [8, 10]. Several lines of evidence strongly suggest that aging is a continuous biological process during which progressive changes in CV structure, physiology, and biochemistry occur and negatively impact cardiac function and contribute to HF [8, 10]. Taken together, these characteristic changes can provide the rational basis for identifying targets for specific interventions during the aging process with the goal of preventing the march to HF.

Telomeres, Telomere Length and Telomerase Activity, and Implications for Prevention

Evidence since the 1990s suggest that telomeres serve as a mitotic clock [28] and mean telomere length may serve as a marker of biological aging at the cellular level [29] that is heritable [30]. Telomeres are DNA-protein complexes at the ends of chromosomes that maintain chromosome stability and control cell cycles [31]. In humans, telomeres consist of repeats of DNA sequences of six nucleic acid–base pairs, with TTAGGG on one strand and AATCCC on the other strand. Telomere length is genetically determined [30], and every individual appears to have a characteristic length in different organs [32]. During aging, telomeres get progressively shorter with every cell division [33], decreased telomere length to a critical value triggers cellular senescence [31], and shorter telomeres mark increased biological age [29]. Increased oxidative stress is an important mechanism for increased telomere loss per cell division and cellular aging [34] and aging-related CV diseases such as hypertension [35] and homocysteine-induced endothelial senescence [34]. In the latter study, increased levels of pro-atherogenic intracellular adhesion molecule-1 (ICAM-1) and plasminogen activator inhibitor-1 (PAI-1) correlated with the degree of endothelial senescence [34]. A second mechanism for telomere attrition involves inflammation. For example, stem cell cultures enriched with cytokines such as interleukin-6 (IL-6) and stem cell factor (SCF) show increased telomere attrition [29]. In a population of men and women aged 35–55 years and free of overt CV disease, increased levels of inflammation and oxidative stress markers such as IL-6 and hs-CRP (as well as fibrinogen in men and oxidized LDL and uric acid in both genders) were associated with shorter telomere lengths [36].

Aging-Related Telomere Shortening in Cardiovascular Disease from Population Studies

Several population studies [22, 23, 35–48] have documented the association of telomere shortening in circulating leukocytes with aging-related CVDs (Table 2.5). At least eight pertinent points from these studies deserve emphasis:

Table 2.5 Population studies of telomere shortening and aging-related cardiovascular diseases

Diseases [reference]	Age (years)
Coronary artery disease [22]	45–64
Increased risk of myocardial infarction [23]	40–84
Hypertension, insulin resistance, and oxidative stress [35]	40–89
Inflammation and oxidative stress [36]	35–55
Atherosclerosis [37]	42–72
Increased mortality (heart disease, infectious disease) [38]	60–97
Premature myocardial infarction [39]	<50, mean 42.3 ± 5.7
Myocardial infarction in men and stroke [40]	>65, mean 74.2 ± 5.2
Carotid artery atherosclerosis in hypertensive patients [41]	63.6 ± 1.0
Chronic heart failure [42]	66 ± 8.7
Left ventricular dysfunction in the oldest old [43]	84.9–85.7
Type 1 and type 2 diabetes in men [44]	17–48, 24–75
Type 2 diabetes and/or insulin resistance in men [45] ^a	~40–70
Increased pulse pressure and pulse wave velocity in men [46]	56 ± 11
Obesity and cigarette smoking in female twins [47]	18–75
Smoking, obesity, and lack of exercise in low-economic status in female twins [48]	~32–68

^aAll telomere length in leukocytes except for monocytes here in [45]

1. Telomere shortening precedes clinical disease, and the extent of telomere shortening may explain interindividual biological variability in response to CV risk factors (49 for review).
2. Differences in telomere length in individuals with or without CAD are not explained by differences in CV risk factors [49].
3. Individuals prone to CHD are biologically older, with telomere lengths equivalent to those in normal subjects who are 8–12 years older [22, 37, 39].
4. Telomere lengths are longer in women than men [46] suggesting that for a given chronological age, biological age is more advanced in men and may be linked to the effect of estrogens on telomerase activity [50].
5. Increased oxidative stress and inflammation may play a major role in telomere shortening and progression of CVD [35, 36, 44, 45].
6. In HF patients, shorter telomere lengths correlate with greater severity of atherosclerotic heart disease [42].
7. Marked telomere shortening may play a role in the pathogenesis of type 1 diabetes via increased pancreatic inflammation [44].
8. A study of chronic stress arousal in healthy women suggested that low leukocyte telomerase activity may be an earlier marker of CV risk than telomere shortening [51].

Telomere Shortening and Cellular Senescence in Human Pathological Studies

Several human pathological studies of aging have documented shortened telomeres, including in different tissues of the same individual [32]; coronary endothelial cells of arteries from autopsied hearts with CHD [52]; atherosclerotic cells in intima and media of autopsied abdominal aortas, especially at distal sites [53]; vascular smooth muscle cells in atherosclerotic plaques, cell cycle inhibitor p16^{INK4a} positive and c-Kit-positive cells, and myocytes [54]; and dilated cardiomyopathy [55]. While telomere shortening associated with CHD and other CVDs during aging can be explained by increased cell turnover and replicative stress that occur in these diseases, emerging evidence suggests that it

may play a role in their pathogenesis. Thus, early atherosclerotic plaques show early evidence of endothelial [56] and smooth muscle [54] cell senescence and increased expression of intracellular adhesion molecule-1 (ICAM-1) and decreased endothelial nitric oxide synthase (eNOS) that are implicated in atherogenesis [57]. These findings support the telomere hypothesis (49 for review) that short telomeres contribute to coronary and CVD risk through cellular senescence.

Telomere Shortening and Heart Failure

Telomere shortening may also contribute to HF. In human end-stage HF, cardiomyocyte apoptosis is associated with downregulation of specific telomere repeat-binding factor TRF-2, activation of checkpoint kinase Chk2 that is linked to DNA damage and apoptosis, and telomere shortening [58]. Experimentally in cultured rat cardiomyocytes, suppression of TRF-2 triggers telomere shortening, Chk2 activation, and apoptosis, whereas exogenous TRF-2 confers protection from oxidative stress [58]. Mechanical stress induced by aortic constriction in mice results in telomere shortening, downregulation of TRF-2, and Chk2 activation as in human HF [58]. Forced transgenic expression of telomerase prevented telomere shortening, downregulation of TRF-2, activation of Chk2, and apoptosis [58]. Together, these findings implicate telomere dysfunction via stress-induced downregulation of TRF-2 in HF [58]. Furthermore, telomerase knockout mice develop short telomeres and HF [59], suggesting that telomere shortening with aging contributes to HF and may be targeted for therapy.

Stress Protein and Aging-Related Cardiovascular Disease

Studies of aging animals are unique in that they are protected from the usual environmental risk factors. In a recent study, LV proteomic analysis in aging mice revealed that several stress proteins associated with aging and CV disease, such as mortalin, peroxiredoxin-3, epoxide hydrolase, and superoxide

dismutases SOD-1 (Cu/ZnSOD) and SOD-2 (MnSOD), can differentiate between young, middle-aged, and old mice [60] and may therefore serve as potential markers of cardiac aging. However, telomere lengths were not measured in that study.

Preserved Telomere Length and Healthy Aging

While telomere shortening has been linked to cellular aging and CV disease, preserved telomere length appears to reflect healthy aging. Three recent population studies that addressed healthy aging and longevity deserve mention. First, in elderly individuals aged 70–79 years, shorter telomere length correlated with poorer health status and survival and shorter life spans, suggesting that telomere length may be a biomarker of survival and healthy aging [61]. Second, gene expression profiles in individuals aged 57–97 years demonstrated that cell division cycle 42 (CDC42) and coronin (CORO1A) are strongly associated with biological age and survival, and gene expressions that increase with age were associated with

increased mortality, whereas those that decrease with age were generally associated with reduced mortality [62], thereby supporting a genetic contribution to longevity. Third, in individuals aged 20–59, ≥90, and ≥98 years, three genes (HRAS1, LASS1, and APOE) that reduce age-related lipotoxicity were associated with increased survival, and LASS1 appeared to contribute to healthy aging and greater survival in the tenth decade of life [63]. Unfortunately, neither of the latter gene studies measured telomere lengths [62, 63].

The Aging Continuum, Cardiovascular Risk Exposure, and the March to Heart Failure

Population studies have established the role of environmental, lifestyle, and genetic factors in the development of hypertension (CAD and HF) [1–4]. During the aging continuum, lifelong exposure to the adverse influence of CV risk factors can lead to pathophysiologic alterations that converge and contribute in the march to HF (Fig. 2.1). Major risk factors include age, genetic factors, diet,

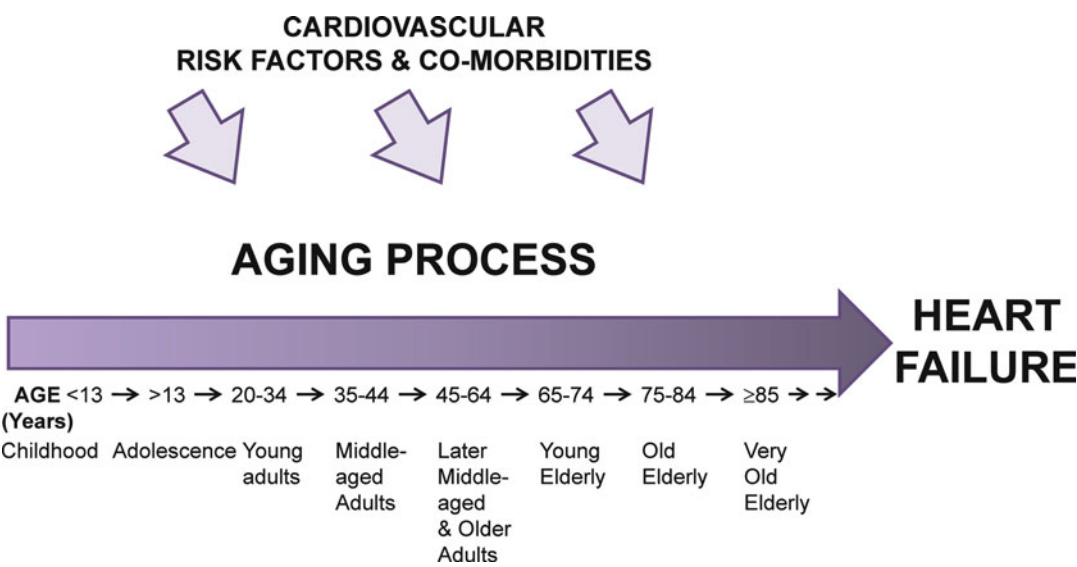


Fig. 2.1 Prevention and the march to heart failure during aging. Lifelong exposure to cardiovascular risk factors during the aging process, as well as comorbidities in later stages, fuels the relentless march to heart failure. It is proposed that, for maximal benefit and to promote healthy aging, preventive measures need to be applied throughout

the aging process and begin early. Additionally, therapy should target different age subsets during the aging-heart failure continuum (reprinted from Jugdutt BI. Prevention of heart failure in the elderly: when, where and how to begin. Heart Fail Rev 2012; 17:531–544. With permission Springer Science + Business Media)

smoking, sedentary lifestyle, stress, dyslipidemia, and exposure to toxins. In this construct, fundamental physiological, biological, and structural changes associated with CV aging itself lead to increased fibrosis, increased ventricular-arterial stiffening, ventricular diastolic dysfunction, and HF with preserved ejection fraction [8–11, 19–21]. In addition, interactions among CV risk factors and the aging heart substrate compounded by the effect of comorbidities can be expected to act in concert and further fuel the march to HF. Major comorbidities include hypertension, CAD, type 2 diabetes, metabolic syndrome, and obesity. In fact, population studies have shown that the interactions between CV risk factors and the aging CV system lead to vascular disease progression. Such is the case with hypertension. Several CV risk factors lead to hypertension, which in turn interacts with other risk factors and comorbidities resulting in complications and end-organ pathologies, including stroke, myocardial infarction, HF, and renal failure [4]. Not surprisingly, the risk of HF increases steeply in the presence of antecedent hypertension and myocardial infarction [4].

The Aging Continuum, Cardiovascular Risk, and Implications for Prevention

Pertinent in the context of prevention, prolonged exposure to CV risk factors during aging has a cumulative effect on CVD progression, and the risk of end-organ damage and HF increases with age [64, 65]. This is true among non-elderly and elderly groups and is borne out in many studies. For example, in a population study spanning two decades (1975–1995), Goldberg et al. showed that the risk of myocardial infarction increases progressively across three elderly subgroups: the younger elderly aged 65–74 years, the older elderly aged 75–84 years, and the very elderly aged >85 years [66]. The more recent INTERHEART study that ranked potentially modifiable CV risk factors for myocardial infarction in five age groups ranging from younger adults to the older elderly (<45, 46–55, 56–65, 66–70, and >70 years) showed a similar trend [67].

A leading pioneer of preventive cardiology, the late Dr. William B. Kannel, who led the Framingham Heart Study (FHS) from 1966 to 1979 [68], was among those who are credited with coining the term “coronary risk factors” [69]. Kannel played a major role in identifying correctable predisposing CV risk factors [70]. In a longitudinal study of 186 men and women aged between 30 and 59 years, Kannel and associates confirmed the association of three risk factors (hypertension, hypercholesterolemia, and electrocardiographic evidence of left ventricular hypertrophy) with increased risk of CHD over a 6-year period [69].

At least five other population studies expanded the list of risk factors and documented the lifetime risk of coronary heart disease [71–73], including in the oldest old [74]. In one FHS cohort of 7,733 men and women, the lifetime risk of CHD (defined by angina pectoris, coronary insufficiency, myocardial infarction, or coronary death) increased from 1:2 for men and 1:3 for women at age 40 years to 1:3 for men and 1:4 for women at age 70 years [71]. In another FHS cohort of 3,564 men and 4,362 women without atherosclerotic CV disease (defined by angina, coronary insufficiency, myocardial infarction, stroke, claudication) and absence of risk factors (based on normal body mass index and absence of smoking, hypertension, hypercholesterolemia, and diabetes) at age 50 years was associated with low lifetime risk for CV disease to age 95 years and longer survival [73]. In a third FHS cohort of 3,757 men and 4,472 women aged 35–84 years and without HF followed for 25 years (1971–1996), the overall lifetime risk of HF was 1:5 in both men and women and 1:9 for men and 1:6 in women without antecedent myocardial infarction [64]. In a fourth FHS cohort of 2,302 men and women with mean age 44 years, the presence of parental CV disease predicted the risk of future events in the middle-aged adults over 8 years [72]. In a fifth FHS cohort of 2,531 men and women aged 40–50 years and followed to the age of 85 years, lower levels of key CV risk factors (electrocardiographic evidence of left ventricular hypertrophy, body mass index, blood lipids, smoking, glucose intolerance, physical activity,

and alcohol intake) at middle age predicted survival and major morbidity-free survival to age 85–100 years [74]. Collectively, these five studies support education, screening, early recognition, and treatment of CV risk factors [71–73], with attention to family history [72] and aggressive measures to control hypertension and prevent myocardial infarction [64] and delay or prevent aging-related morbidity and mortality [74] in both young adults and the elderly.

Clustering of Cardiovascular Risk and Implication for Prevention

Kannel also underscored the clustering of major risk factors on the basis of long-term epidemiological data over six decades in the FHS [70], implying metabolic linkage as pertinent for the metabolic syndrome. Major risk factors for CAD in the Framingham Risk Score (FRS) included age, hypertension, cigarette smoking, diabetes mellitus, and hyperlipidemia [69, 75, 76]. This multivariable CV risk algorithm was later expanded to include sex, levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and treatment of hypertension to estimate the risk of myocardial infarction or death as a result of CHD [77–80]. The Reynolds Risk Score (RRS) which added parental family history of premature coronary heart disease and high-sensitivity C-reactive protein (hs-CRP) to the traditional risk factors provided additional predictive information for subclinical atherosclerosis compared to the FRS in women [81, 82] and men [83]. The risk algorithms were further expanded with increasing knowledge of the biology of CV risk and atherosclerosis, atherothrombosis, inflammation, endothelial dysfunction, plaque rupture, metabolic syndrome, and aging. Several epidemiological studies confirmed the risk factors for CAD and further expanded the list to include age (a major determinant), male sex, cigarette smoking, diabetes, cholesterol (TC, LDL-C, ApoA-1, or ApoB), HDL-C, blood pressure, family history of premature coronary disease (age <60), and added inflammatory biomarkers such

as hs-CRP, hyperglycemia, glycated hemoglobin-A_{1c} (HbA_{1c}), creatinine, homocysteine, overweight, obesity, poor nutrition, calorie excess, physical inactivity, and psychological stress. Emerging factors proposed for improving risk prediction include the metabolic syndrome [84], chronic kidney disease [85], and chronic inflammatory diseases (such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis) and chronic HIV that need further evaluation [86]. Other studies have underscored the importance of family history in coronary artery calcification [87], a high body mass index (BMI) [88], and statin therapy for reducing cholesterol [89] and inflammatory markers [90, 91].

In the last paper before his death in 2011 at age 87 [79], Kannel emphasized the importance of multivariable risk factor influences on CVD, including CAD, stroke, peripheral artery disease, and HF. Kannel therefore favored use of multivariable risk factor assessment in primary care and noted that 40–50 % of people having CV events are not considered high risk by most current risk profiles [70]. Interestingly in INTERHEART, nine factors accounted for most of the risk of myocardial infarction; the factors were smoking, fruit and vegetable intake, exercise, alcohol intake, hypertension, diabetes, abdominal obesity, psychosocial, and blood lipid levels as ApoB/ApoA-1 ratio [67].

The collective evidence indicates that several CV risk scoring systems, such as the FRS and RRS systems, provide best estimates of the probability of individuals to develop CVD with aging over the subsequent 5 or 10 years and those most likely to benefit from prevention. For example, the FRS can be used to categorize individuals as low risk (≤ 10 %), intermediate risk (10–20 %), and high risk (≥ 20 %) for CAD at 10 years. Importantly, in every algorithm, age is the strongest predictor of CV risk, and nearly all elderly individuals aged ≥ 70 years and nearly none of adults aged <40 years are at high risk. It follows that adults aged >40 years are mostly likely to benefit from preventive measures (such as smoking cessation, healthy diet, and regular exercise) and the elderly mostly likely to benefit from preventive medical therapy (such as antihypertensive

agents, cholesterol-lowering agents, and low-dose aspirin). A recent study reported a decrease in coronary heart disease mortality rates between 1994 and 2005 that was associated primarily with trend in risk factors (decreased blood pressure and cholesterol, increased diabetes and BMI) and improved medical treatments for hypertension and hyperlipidemia [92].

Biomarkers and Cardiovascular Risk and Implication for Prevention

Kannel also suggested that risk assessment may be improved by use of biomarkers, genetic markers, and vascular imaging and biomarkers may be useful for assessing the benefits of therapy and stratifying those with intermediate CV risk [70]. Indeed recent studies suggest that biomarkers [91, 93–100] and vascular imaging [87, 101–103] can stratify subgroups at risk of CVD [87, 101–103] and HF [95–99] and guide HF management [97]. Importantly, evidence suggests that several biomarkers [91, 93–100] including hs-CRP [91], N-terminal pro-B-type natriuretic peptide (NT-proBNP) [95–97], cardiac troponin I (cni) [98], and cardiac troponin T (cniT) [95, 99] can be used to predict HF [95–99], adverse remodeling [97], and CV death in older adults and the elderly [95, 98, 99]. In one study of young elderly patients with chronic systolic HF (mean ages 66 and 67 years), high serum levels of cortisol and aldosterone were shown to be independent predictors of increased mortality risk [104].

Although a strategy to suppress NT-proBNP levels in older adult patients (mean age 63 years) with chronic systolic HF has been shown to reduce adverse events compared to the standard approach [97], BNP levels may not distinguish patients with systolic and diastolic HF. Thus, a recent study showed that elderly patients (mean age 70 years) with diastolic HF had similar although less severe pathophysiological characteristics than those with systolic HF, including BNP levels [105]. However, among predominantly elderly patients (mean age 70 years, range 18–105) presenting to the emergency department with congestive HF, BNP levels were lower in

those with non-systolic HF than those with systolic HF but provided only modest discrimination of the subgroups compared to traditional parameters and felt to be best for distinguishing patients with or without congestive HF [106]. In another report of older adults presenting to the emergency department with congestive HF (mean age 64 years) in REDHOT, BNP levels predicted 90-day outcomes and aided stratification and triage [107]. Taken together, judicious application of biomarkers can be used to guide efforts to reduce CV risk on an individual basis during aging, and biomarkers such as NT-proBNP can guide measures to reduce hospitalization in elderly patients with HF.

Comorbidities in Aging-Related Heart Failure: Hypertension and Myocardial Infarction

As reviewed before [10], hypertension and myocardial infarction are prevalent in the elderly and the two major contributors to HF in that population segment. Importantly, hypertension results in predominantly diastolic HF, or HF with preserved systolic function or preserved ejection fraction (HF-PEF), whereas myocardial infarction results in predominantly HF with systolic dysfunction or low ejection fraction (HF-low EF) [10]. Whereas most myocardial infarctions are due to coronary artery disease, hypertension involves renal, vascular, neural, and humoral mechanisms as well as genetic and various behavioral factors. An early study on patients in the SOLVD registry underscored the importance of decreased ejection fraction as a major factor in neurohormonal activation in patients with HF [108]. Hypertension is also a major risk factor for coronary heart disease, left ventricular hypertrophy, and HF. Since both aging and hypertension are associated with left ventricular hypertrophy, fibrosis, and diastolic dysfunction (Table 2.2), the elderly with hypertension is at enhanced risk for HF-PEF. Similarly, the elderly patient with myocardial infarction and cardiac changes associated with aging (Tables 2.3 and 2.4) is at enhanced risk for severe

HF-low EF. Hypertensive patients with myocardial infarction develop mixed left ventricular hypertrophy and HF-low EF. While management guidelines for elderly hypertension [109] and elderly acute non-ST-elevation and ST-elevation myocardial infarction [16, 17] have been developed and the guidelines for HF management in adults mention the elderly [110], specific detailed management guidelines for that growing elderly population with HF are lacking.

Comorbidities in Aging-Related Heart Failure: Type 2 Diabetes, Metabolic Syndrome, and Obesity

Besides hypertension and myocardial infarction, several other comorbidities prevalent in older adults and the elderly such as type 2 diabetes, metabolic syndrome, and obesity amplify CV risk. Numerous studies have shown that these comorbidities accelerate the progression toward vascular complications and end-organ pathologies, including stroke, myocardial infarction, HF, renal failure, peripheral arterial disease, disability, and death [84, 86, 111]. In the USA, the prevalence of obesity (defined as BMI > 30 kg/m² in adults) nearly doubled (from 15 % to 33 %) over the last 24 years, and nearly 67 % are either overweight or obese [112]. Also in the USA, the lifetime risk of diabetes increased between age 35 and 70 years and plateaued thereafter [113]. The overall risk of diabetes ranges from 35 % to 45 % in men and 30 % to 55 % in women. Elderly patients with diabetes and hypertension were shown to have higher mortality [114, 115]. Diabetes also increases the risk of HF in the elderly [116]. The ONTARGET/TRANSCEND study of high-risk elderly patients showed that the fasting blood glucose was an independent predictor of HF hospitalization [117] and supported lowering of blood glucose to reduce HF risk [118]. The ONTARGET/TRANSCEND study also showed the clinical effectiveness of therapy with the angiotensin II receptor blocker telmisartan for controlling hypertension and vascular risk in the elderly [65].

Several studies have established that the increased CV risk with type 2 diabetes is due to high blood glucose levels. High glucose levels have been implicated in microvascular damage, and several pathways of vascular glucotoxicity have been identified [119, 120]. The longitudinal STENO-2 study of CV risk reduction in high-risk older adult and young elderly patients (aged 50–66 years) with diabetes using a multifactorial intervention involving tight glucose regulation and renin angiotensin blockers, aspirin, lipid-lowering agents, and behavior modification over 7.8 years showed sustained decrease in vascular complications and deaths from CV and any cause during follow-up over 5.5 years [121]. It is pertinent to note that in STENO-2, the mortality curves for intensive versus conventional therapy took 8 years to diverge [121], suggesting that diabetes is a long-acting risk factor that affects multiple systems and needs to be targeted early with long-term glycemic control. High blood glucose and HbA_{1c} are important biomarkers of CV risk in diabetes. Although hyperglycemia is common after myocardial infarction and is a predictor of adverse outcomes, firm guidelines await completion of randomized clinical trials [122]. Data in the elderly and very old with HF and diabetes is lacking.

Comorbidities in Aging-Related Heart Failure: Atrial Fibrillation

Another important comorbidity in the elderly is atrial fibrillation; it is not only common in the elderly [123, 124] but also worsens HF [125] and results in additional complications such as embolism and stroke [126]. The median age of patients with atrial fibrillation is about 75 years, and nearly 70 % are aged between 65 and 85 years [126]. Atrial fibrillation is more prevalent in men and doubled in men compared to women between the 1970s and 1990s [127]. It is also more prevalent in Caucasian than Afro-Americans with HF [128] and is approaching epidemic proportions [129]. Pertinent for primary prevention, the main conditions associated with atrial fibrillation include hypertension, ischemic heart disease, HF,

valvular heart disease, and diabetes [130]. Importantly, the risk of new atrial fibrillation in elderly patients aged ≥ 65 years is nearly 2 % per year [131]. Furthermore, regardless of treatment, survival is worse in elderly patients aged ≥ 65 years with atrial fibrillation and a history of concomitant coronary artery disease or abnormal LV ejection fraction [132].

Chronological Definition of Elderly, Biological Aging, and Implications for Prevention

In the context of the aging continuum hypothesis, definition of elderly by an arbitrary age is not logical. The original definition of the elderly by the chronologic age of 65 years was only adopted by default and based on socioeconomic and political factors prevalent in the late 1800s rather than on the biology of aging [9]. Nevertheless, even this arbitrary chronological cutoff was subsequently found to have clinical relevance as early trials showed that not only the prevalence of hypertension increases progressively with aging but also the vascular complications associated with the disease increased sharply after the age of 65 years, including stroke, myocardial infarction, HF, and renal failure [4]. However, despite exposure to similar CV risk factors and risk profiles, a common finding in clinical practice is that individuals differ in susceptibility, age of onset, and rate of progression of CVDs, including hypertension, CAD, and HF. Clinical scenarios of young adults developing severe CAD or very elderly individuals having normal or low CV risk scores are fairly frequent. Such interindividual variability can be explained by a genetic predisposition or protection to CVD and genetically determined variability in biological aging.

Prevention Considering Biological Aging and the Aging Continuum

Further to the foregoing discussions, prevention of HF in the elderly should be a healthcare priority. Appropriate preventive measures need to be

urgently formulated and implemented to reduce the burden of the rising HF prevalence and related complications in elderly men and women of tomorrow. In formulating strategies, it is important to recognize that CV aging is a continuous lifelong process and is risky because concomitant lifelong exposure to adverse CV risk factors throughout the process fuels the march to HF (Fig. 2.1). Efforts need to be focused on promoting healthy aging and preventing development of CVDs that contribute to HF.

When and Where to Begin?

Three critical areas need consideration in planning preventive strategies to reduce the growing burden of HF in the elderly: (1) biological factors in aging-related HF, (2) pathophysiological causes of aging-related HF, and (3) major CV risk factors and comorbidities that impact aging-related HF. From the collective evidence about the pathobiology and pathophysiology of CV aging and aging-related HF (Tables 2.3 and 2.4) and the data from population studies, it is clear that to achieve fullest impact in reducing the burden of HF in the growing aging population, preventive strategies need to address the entire aging-HF continuum and the cumulative impact of lifelong exposure to CV risk factors. Ideally, preventive measures should be applied during the entire lifetime and before individuals reach the chronological elderly age. The prevention measures need to target major CV risk factors as well as major comorbidities early during the aging continuum. In addition, it is important to recognize that the rate of biological aging can differ markedly among individuals and impact disease onset and progression irrespective of gender or ethnicity.

How to Begin?

There are three logical steps. The first step is to acknowledge the increasing trend in the elderly population with HF and the potential implication for healthcare systems. The second step is to have

a clear understanding of the major contributors to the problem. The third step is to plan strategies for addressing the problem in its entirety. In its broadest sense, implementation of conventional primary and secondary prevention measures should begin in early childhood and span adolescence and young and older adulthood in order to maximally reduce the negative effect of adverse CV risk factors, interrupt the march to HF, and reduce HF in the elderly groups (Fig. 2.1).

Benefits of Prevention and Healthy Aging

The potential benefits of healthy aging for the healthcare system are obvious. The benefits of decreased HF hospitalizations for adult and elderly patients in terms of healthcare cost savings alone would be staggering. Aggressive implementation of the published guidelines for optimal management [5, 77, 109, 110, 121, 125, 133] and prevention [79, 133–137] of CVD is needed to reduce HF hospitalizations [138]. The AHA statements have emphasized implementation of guideline-driven interventions at early stages of HF [5, 137]. Recent management guidelines have also addressed the two major contributors to HF in the elderly, namely, hypertension [106] and myocardial infarction [16, 17]. However, while the guidelines for hypertension in elderly patients were based on data from randomized clinical trials that included older age groups, this was not the case for myocardial infarction and HF. Pending more evidence-based data in elderly HF patients, the principles for secondary prevention of HF in adults can be adapted to the elderly provided specific issues are addressed, including multisystem aging, comorbidities, polypharmacy, frailty, and psychosocial factors, especially in the oldest old [10, 11, 65, 139]. While guideline-driven management of hypertension decreased HF in the elderly [140], including the oldest old [141, 142], caution is prudent with other therapies in that group. Thus, adverse drug events account for most emergency hospitalizations for HF among elderly Americans (aged 65 to ≥ 85 years), especially involving

warfarin, insulins, oral antiplatelet agents, and oral hypoglycemic agents [143], suggesting the need for improved management of antithrombotic and antidiabetic drugs in the elderly.

As for primary prevention of CV diseases that lead to HF, the AHA guidelines address mainly adults, aged ≥ 40 years. They recommend early risk intervention and emphasize smoking cessation, blood pressure control, healthy diet, aspirin, blood lipid management, physical activity, weight management, diabetes management, and management of chronic atrial fibrillation [134]. All guidelines have emphasized lifestyle management, especially smoking cessation, physical activity, and healthy diet with caloric restriction in adults and the elderly [137], and its benefits were evident when implemented in adults [144]. Although evidence supports caloric restriction for healthy CV aging [145] prolonged longevity [146], this is not aggressively implemented. Ideally, primary prevention should begin in early childhood and include adults aged < 40 years before the appearance of overt CV disease.

Role of Education in Prevention

Education is key in prevention. The HF prevention guideline emphasizes the value of physician education for increasing awareness [137]. The US education program for hypertension started in the 1970s was very successful [147]. A Canadian healthcare professional education program started in the mid-1970s increased the diagnosis and treatment of hypertension [148], reduced the gender gap in treatment [148], and encouraged more aggressive hypertension management in the elderly [149]. However, even with tight blood pressure control, hypertensive patients remained at increased risk for stroke and myocardial infarction due to undertreatment of other CV risk factors [150]. Education reinforcing comprehensive management of CV risk factors using risk scores and biomarkers is therefore needed.

Despite a worldwide decrease in systolic blood pressure through education and therapies since 1980, systolic blood pressure remains high among low-income and middle-income countries

[151], suggesting the need to target those groups via education programs and/or additional measures to decrease the global HF burden. Prevention guidelines have emphasized ethnic differences and higher prevalence of adverse CV risk factors, including smoking, sedentary lifestyle, and high saturated fat diets [137], suggesting that those groups also need to be targeted in education programs. In a Canadian study of HF hospitalizations, Chinese patients were older and had the highest rates of renal disease and higher 1-year mortality than white patients, whereas East Indian patients were youngest and had the highest rates of ischemic heart disease and diabetes and similar mortality as white patients [152]. Education can be a powerful tool for primary prevention. Simply providing understandable calorie information via posted signs to low-income black adolescents resulted in a decrease in purchases of sugar-containing beverages, thereby reducing calorie intake [153].

Conclusions

The elderly population is increasing worldwide and the burden of HF is greatest in the elderly. Morbidity and mortality from CVD and comorbidities in the elderly and related healthcare costs are increasing at an alarming pace. Several biological markers correlate with the aging phenotype and HF. Low telomerase activity and telomere shortening may be early markers of aging-related CVD and can be used to guide preventive strategies. It is important to appreciate that CV aging is a continuous lifelong and risky process because concomitant lifelong exposure to adverse CV risk factors throughout the process fuels the march to HF (Fig. 2.1).

There is urgent need for identifying new therapeutic targets through translational research for optimizing HF therapy in the elderly as well as delay and/or retard CV aging. Efforts need to be directed on promoting healthy aging and preventing development of CVDs that contribute to HF. Legislation is needed to reduce lifelong exposure to CV risk factors, including toxins and pollutants

we inhale, ingest, or are exposed to from our external environment and transfer to our internal environment. For secondary prevention, more clinical trial data is needed to identify optimal HF therapies for different aging subgroups ranging from young adults to the elderly and very old based on the new advances in the pathobiology of aging-related HF and use of biomarkers of biological aging. Education programs should reinforce comprehensive management of CV risk factors using risk scores and biomarkers. For primary prevention, programs should target all age groups including children, adolescents and young adults, and older age groups. In its broadest sense, education programs should be aimed not only at physicians and healthcare personnel but also at the public of all age and ethnic groups, both genders, and teachers as well as children, adolescents, and young adults in schools and universities. Education can be a most powerful tool for both primary and secondary prevention. Strong emphasis should be placed on education from early childhood and adolescence about the role of exposure to adverse CV risk factors in the march to HF and how this can be halted and thereby promote healthy aging.

Acknowledgement This work was supported in part by grant # IAP-99003 from the Canadian Institutes of Health Research, Ottawa, Ontario. I am indebted to Catherine Jugdutt for her assistance.

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Aging and Heart Failure

Mechanisms and Management

Jugdutt, B.I. (Ed.)

2014, XXII, 475 p. 84 illus., 50 illus. in color., Hardcover

ISBN: 978-1-4939-0267-5