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Sex Differences in Myocardial and Vascular Aging

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Abstract

It is well known that cardiovascular disease (CVD) manifests differently in women and men. The underlying causes of these differences over the aging lifespan is less well understood. Sex differences in cardiac and vascular phenotypes are seen in childhood and tend to track along distinct trajectories related to dimorphism in genetic factors as well as response to risk exposures and hormonal changes over the life course. These differences underlie sex- specific variation in cardiovascular events later in life, including myocardial infarction, heart failure, ischemic stroke, and peripheral vascular disease. With respect to cardiac phenotypes, females have intrinsically smaller body-size-adjusted cardiac volumes and then tend to experience greater age-related wall thickening and myocardial stiffening with aging. With respect to vascular phenotypes, sexual dimorphism in both physiology and pathophysiology are also seen, including overt differences in blood pressure trajectories. The majority of sex differences in myocardial and vascular alterations that manifest with aging appear to follow relatively consistent trajectories from the very early to the very later stages of life. This review aims to synthesize recent cardiovascular aging-related research to highlight clinically relevant studies in diverse female and male populations that can inform approaches to improving the diagnosis, management, and prognosis of CVD risks in the aging population at large.

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INTRODUCTION

Sex differences in cardiovascular phenotypes are frequently recognized from cross-sectional studies as well as studies that have examined differences in the incidence and longer-term outcomes for a variety of cardiovascular disease (CVD) conditions. Whereas many differences in CVD outcomes arise from factors related to gender, which is based on socially constructed features, we will focus predominantly on differences in both outcomes and pre-clinical characteristics that arise from factors related to sex, which is based on biologically defined traits.[1] There is now a large and compelling body of data indicating that biological sex is directly and significantly related to differences in cardiovascular traits. From emerging evidence, we are now beginning to understand that these differences likely emanate from intrinsically distinct phenotypic "starting points" that precede age-related changes, combined with divergent trajectories that appear mediated by female-male differences in the response to various risk exposures. These elements represent the complexity of interactions between sex, risk exposures, and time-dependent pathophysiology, which contribute in aggregate to consistently observed patterns in how women and men tend to manifest subclinical as well as clinical forms of CVD differently.[2] Herein, we review several features of the accumulating research on cardiovascular aging, including information relevant to our understanding of age-related cardiac phenotypes, vascular phenotypes, and the role of hormones. The goal of this review is to highlight key aspects of our current understanding of sex differences in myocardial and vascular aging and identify potential future directions.

Sex and the Mechanisms of Cardiovascular Aging

At the outset, it is important to recognize that most insights pertaining to cardiovascular aging arise from what is now a robust foundation of geroscience. Accordingly, the complexity of molecular mechanisms underlying common chronic diseases of aging has been extensively discussed, with multiple conceptual as well as analytical models proposed.[3] One seminal and often referenced scheme, known as "The Seven Pillars of Aging", highlights key interconnected processes that include epigenetics, macromolecular damage, proteostasis, metabolism, stem cells and regeneration, inflammation, and adaptation to stress.[4] This framework has been expanded and translated through prior efforts aimed at clarifying the mechanisms that are relevant to aging of the cardiovascular system and the development of common age-related CVD phenotypes.[5-7] The same framework can be further adapted for understanding sex-based variation in the mechanisms of cardiovascular aging that contribute sex differences in manifest cardiovascular aging phenotypes (Figure 1). Notwithstanding the relative paucity of data in this nascent field, there are some general themes that have emerged from across experimental, translational, and clinical investigations. The first theme is centered on how intrinsic genetic factors influence sex variation in life course trajectories of cardiovascular phenotypes, based on an abundance of data and that sex differences in traits such as lipid profiles and intima-medial thickness are seen as early as childhood and prepuberty.[8-10] The second general theme is a relative excess

versus relative deficiency of molecular processes with potential to preserve myocardial integrity in females versus males, respectively (Table 1). In turn, the correlative myocardial phenotypes that tend to dominate with advancing age are concentric versus eccentric left ventricular (LV) phenotypes in women compared to men. The third general theme is a heightened vascular sensitivity to a variety of mechanistic stressors in females that likely contributes to accelerated vascular aging phenotypes seen in women; notably, propensity for severe forms of certain vascular diseases exists earlier in life for males – in whom vascular aging trajectories are present but less pronounced. In the next sections, we will review the reported evidence regarding myocardial and vascular aging phenotypes that tend to exhibit sexual dimorphism in the context of these two themes, while also providing special attention to the aging phenotypes that predominate in women (Figure 2). For additional reference, we provide a summary of the human observational and trial studies that have offered data relevant to all the findings discussed (Table 2).

Sex-Related Differences in Myocardial Aging

Mechanisms.—Myocardial aging encompasses multiple changes occurring over the human lifespan. Extending predominantly from sex-biased in gene expression in addition to sex chromosomal differences and potentially epigenetic factors,[11-13] sex-based differences in myocardial aging trajectories include molecular, cellular, and interstitial changes that eventually result in macroscopic differences in size, shape, and function of the heart. Cellular longevity, in general, tends to exhibit intrinsic sex differences with males compared to females having consistently shorter telomeres, less robust mitochondrial function, and higher likelihood of deleterious somatic mutation.[14-16] Accordingly, relative differences specific to myocyte aging trajectories are also seen. Relative to the female phenotype, the male myocytes undergo both more cellular loss and reactive hypertrophy due to increased necrosis and apoptosis.[17,18] Some of these sex differences may well be mediated in early- to mid-life by estrogen and its derivatives, which have been shown to attenuate injury from ischemia and reperfusion,[19-21] mitigate reactive oxygen species damage by modulating mitochondrial activity,[22] and reduce cardiac fibroblast activation in part by downregulating collagen and matrix metalloprotease production and modifying the micro-RNA regulated fibrotic response to inflammation.[23-26] The direct effects of relative estrogen loss in later life are uncertain. However, in murine models, extracellular matrix composition shifts distinctly between young and old female hearts in comparison to male hearts in terms of collagen composition.[23,25] In particular, the ratio of collagen to elastin is significantly increased in females with the shift towards higher collagen production in the myocardial extracellular matrix.[24,25]

Myocardial Phenotypes.—Consistent with the recognition that sex-biased gene expression is relevant to multi-organ system phenotypes,[13] there is clear evidence that females and males exhibit differences in cardiac morphology from early in life. Accordingly, normal values for cardiac chamber dimensions have long been reported in the setting of sex-specific reference limits by cardiac imaging and radiology specialists according to evidence-based guidelines.[27] In turn, the patterns of cardiac aging (i.e., age-related cardiac remodeling) also differ by sex. When cross-sectionally compared to men, healthy appearing middle-aged to older-aged adult women have smaller left ventricular (LV) dimensions and

lower stroke volumes, even after accounting for body size.[28] Longitudinal differences are also seen, with women exhibiting higher age-related relative wall thickening[10,27,29,30] and greater age-related systolic stiffening, greater systolic torsion, and greater circumferential shortening of the LV.[31-33] Extending from the sex differences in cardiac remodeling seen in apparently healthy aging, females compared to males demonstrate greater concentric remodeling and diastolic dysfunction in response to stressors such as the afterload stress of aortic stenosis.[34] These trends are observed in the context of more pronounced local inflammation and greater accumulation of predominantly interstitial myocardial fibrosis in females compared to males.[35-37]

Myocardial Outcomes.—Sex-specific changes in myocardial aging at least partly account for the frequently observed sex differences observed in phenotypes of heart failure. Older women are more likely than men of any age to develop heart failure with preserved ejection fraction (HFpEF), even after adjusting for differences in age and the potential effects of survival bias in older aged men compared to older aged women. Consistent data from observational studies and clinical trials have demonstrated that the cardiac aging phenotypes that are more common among women include more pronounced concentric remodeling and greater diastolic dysfunction that can predispose elderly women to HFpEF compared to men.[38,39] The long-term burden of cardiometabolic risk factors have also been hypothesized to contribute to the progressive myocardial remodeling that eventually leads to cardiac dysfunction.[39,40] Women appear more affected by the so-called cardiometabolic type of pre-clinical or clinical heart failure that tends to manifest with advancing age in the setting of hypertension, obesity, type 2 diabetes mellitus, or metabolic syndrome, all of which can also serve to increase risk for HFpEF in particular.[40-44] Notably, women are also less likely to exhibit beneficial remodeling and reversal of LV hypertrophy after treatment for hypertension compared to men.[45] Further reinforcing evidence of sex-specific susceptibility to cardiac disease phenotypes are emerging clinical trials data on sex-specific responsiveness to cardiac disease targeted therapies such as sacubitril/valsartan among many others.[46-48]

Sex-Related Differences in Vascular Aging

Mechanisms.—Vascular aging trajectories manifest in parallel with myocardial aging phenotypes, and also arise from sexual dimorphism in genetic factors.[49] Amidst the multiple mechanisms implicated in overall vascular aging, several features are noted to be more sex specific.[50] At the outset, the vasculature in females compare to males has been found to exhibit greater mineralocorticoid receptor expression[51] and lesser baroreflex sensitivity,[52,53] which set the stage for what appears to be greater salt sensitivity[54] and differential neural-hemodynamic regulation of blood pressure[55] with aging. In addition, in the setting of hormone receptor expression throughout the vasculature,[56-58] studies have found that younger and premenopausal arteries exhibit limited amounts of endothelial inflammation as well as a robust vasodilatory capacity that is mediated by nitric oxide and serves to limit oxidative damage.[59,60] In models and studies of the mid-to-later life vasculature, estrogen decline is associated with endothelial dysfunction dysfunction[59] in the setting of increased reactive oxygen species production,[22,61,62] oxidative stress[22] and nitric oxide suppression.[59] In particular, experimental and physiology data suggest that

reductions in nitric oxide resulting from elevations in oxidative stress contribute not only to endothelial dysfunction but also to arterial stiffening in this setting.[63] Concurrently, there is evidence of a more prominent trajectory in females not only in systemic inflammatory profiles but also inflammation at the cellular level, including reduced anti-inflammatory macrophage activity.[64] These age-related changes, combined with baseline sex differences in vascular diameter even when accounting for body size, appear to promote a greater vascular sensitivity to CVD risk exposures and accelerated atherosclerosis in older women compared to age matched men.[60,65,66 54,59,67-70]

Coronary Vascular Phenotypes.—Patterns of vascular aging differ by sex across the range of vascular beds including the coronary and peripheral vasculature. With respect to coronary disease, women are more vulnerable to endothelial dysfunction and microvascular remodeling and these differences appear to start at a younger age in females than in males. Extensive literature on sex disparities in cardiac disease highlight the increased prevalence of coronary microvascular dysfunction contributing frequently to anginal symptoms in women, who can often present in younger and middle age.[71-73] Extending from abnormalities in vascular function, structural vascular alterations including those derived from the coronary atherosclerotic process also differ by sex across the age spectrum. Younger-aged women have lower calcium scores than younger-aged men but women experience a faster increase in calcification score and progression of calcified plaque with advancing age.[74,75] In the setting of clinical coronary disease, non-culprit coronary artery plaques in women compared to those in men tend to demonstrate greater plaque stability with smaller lipid arcs, fewer cholesterol crystals, and less lesion calcification. These plaques, however, are also more likely to exhibit plaque erosion, which also results in atherothrombotic events.[76,77] Notably, whereas the incidence of thin cap fibroatheroma in women is lower than men before the age of 70, it becomes greater than men after the age of 70.[78] Accordingly, coronary events in women shift from being more erosion-based in younger age to being more rupture-based in older age.[79,80]

Coronary Vascular Outcomes.—Beyond subclinical vascular alterations, which may or may not ultimately present with directly attributable symptoms in many aging adults, the clinically manifest presentations of vascular disease tend to also differ by sex and in ways that are more evident with aging. With respect to coronary disease in particular, women present clinically more often than men with non-obstructive CAD. Non-obstructive CAD, especially when it develops early in life, is much more likely than obstructive CAD to go unrecognized and thus untreated. Thus, after the passage of time, a case of non-obstructive CAD when finally manifest clinically can be found as more diffuse and extensive than a case of obstructive CAD that presents with a similar burden of clinical symptoms. This phenomenon may at least partly contribute to the observed tendency of non-obstructive CAD to promote epicardial and microvascular spasm and conduit vessel stiffening leading to myocardial ischemia. Potentially related to anatomical as well as physiological and pathophysiological sex-specific traits (e.g. females having smaller caliber coronary arteries than men even after accounting for differences in body size), women across the age spectrum are more likely than men to experience angina, ischemia, and acute coronary syndrome in the presence of non-obstructive CAD.[81] Treatment advances

for non-obstructive CAD lag behind those for obstructive CAD. This may be one reason why management of CAD in men has benefitted more from extensive advances in medical and interventional therapies, with accumulating evidence suggesting that CAD incidence and mortality rates have been plateauing and may even be increasing in young and middle-aged women.[82-84]

Systemic Vascular Phenotypes.—Similar to findings for the coronary vasculature, systemic vascular sex differences are also observed. Hemodynamic and neurohormonal factors contribute to age-related alterations in systemic vascular function in both sexes. While maintaining cardiac output and tissue perfusion at levels similar to males, females tend to manifest higher resting heart rates and augmented pulsatile load, particularly with aging. These trends reflect sex differences in age-related changes of dependence on sympathetic versus parasympathetic activation responses to hemodynamic stress and a potentially greater relative hemodynamic load experienced by females compared to males with advancing age.[85-87] Accordingly, several studies have observed accelerated increase in measures of arterial stiffness in females compared to males, beginning in mid-life and most evident during the postmenopausal period.[63,88] With respect to vascular structural changes, males have overall thicker femoral intima-media thickness (IMT) but females demonstrate more pronounced increases in femoral IMT with an increasing number of risk factors, even in the absence of symptoms.[89] Differences in blood pressure trajectories are also noted. Studies also indicate that young and middle aged women have lower baseline blood pressure but more rapid blood pressure elevation over the life course, especially in the setting of cardiometabolic disease states such as hypercholesterolemia and diabetes.[90-93] A similar pattern has been observed for central arterial stiffness. Although the average arterial stiffness is lower in women, it also increases more rapidly in women even after adjusting for body size and aortic diameter.[88,94-96] These vascular differences are clinically reflected in patterns of hypertension prevalence over the life course—prior to age 45, hypertension is more prevalent among men; after age 65, hypertension is more prevalent among women. Collectively, these studies show that although premenopausal women have better overall vascular function than men of similar age, age-related vascular dysfunction progresses at a faster rate in women after controlling for sex-specific basal vascular function.[97,98]

Systemic Vascular Outcomes.—Sex differences in vascular aging patterns, beginning early in life, offer pathophysiological insights into why women manifest vascular outcomes differently – including presenting greater risk for myocardial infarction and stroke risk beginning at lower blood pressure thresholds and consistently experiencing worse stroke outcomes than men.[99,100] Despite these differences seen in observational cohorts, it is worth noting that most published randomized control trials suggest that both sexes derive cardiovascular benefits with intensive control of modifiable risk factors such as blood pressure (Table 2).[101,102] Although these trials were not pre-specified to evaluate for sex differences, and further work is needed to investigate potential sex-specific effects, the results to date are reassuring regarding the derivable benefit of treating hypertension across the lifespan. Perhaps more concerning are the sex differences seen in vascular outcomes for which there exist fewer options for early intervention. For instance, although aortic dissection is more prevalent in males than females, associated mortality is significantly

higher in females.[103] Similarly, although abdominal aortic aneurysm is more common in males than females, females have a significantly greater risk of rupture.[104] For lower extremity peripheral arterial disease (PAD), the prevalence is reported to be similar or greater in women compared to men, although women with PAD have a greater extent of multi-vessel atherosclerotic disease identified at revascularization.[105,106] Late presentation or under-recognition could account for some proportion of each of these disease disparities. However, the consistent theme of a more vulnerable and less stable clinical vascular phenotype in aging women points to the likelihood of common underlying factors – potentially accumulating and augmenting their effects with advancing age.

Hormonal Effects on Life Course Trajectories

A comprehensive examination of sex differences in cardiovascular aging phenotypes involves not only discerning how females and males differ but also a careful consideration of the sex-specific factors that impact aging trajectories – particularly sex hormones. There remains limited data on how age-related decrease in male sex hormones (e.g. testosterone and its metabolite dihydrotestosterone) may be contributors versus biomarkers of age-related CVD risk in men.[107,108] On the other hand, a large body of evidence has emerged regarding the role of ovarian aging – reflected by life course changes in female sex hormones – on age-related CVD risk in women.[109,110] Considered a metric biological aging in females, reproductive longevity can be estimated using a variety of measures (e.g. age at first or last reproduction and age of menarche and menopause). Accelerated ovarian aging (i.e. shortened reproductive longevity) has been linked to epigenetic, metabolic, and oxidative stressors and the development of age-related risk factors as well as both subclinical and clinical CVD phenotypes.[111-116] Accompanying variations in sex hormones have been associated with especially pronounced alterations in glucose metabolism, lipid homeostasis, and adipose tissue distribution in females.[117,118] These findings are concordant with the long-recognized greater risk of cardiovascular outcomes conferred by cardiometabolic risk factors, particularly obesity and diabetes, in women compared to men with or without overt clinical cardiac disease.[119-121]

The Stages of Reproductive Aging Workshop identified ten sequential stages of relatively distinct female sex hormone profiles as representing key phases of biological versus chronological aging in females, with each stage organized as either before or after the final menstrual period – considered the cardinal ovarian aging event.[122] Importantly, across each of these life stages, the age-related decreases in estradiol and increases in follicle-stimulating hormone are known to be progressive, rather than sudden, with variations in longitudinal trajectories that can be used to identify females as having accelerated versus delayed ovarian aging profiles.[123] Concordant with the concept that ovarian aging is more a continuous rather than precipitous process, 10 to 20 year longitudinal studies have found that trajectories of anti-mullerian hormone levels – a measure of ovarian reserve – are associated with worsening lipid profiles as well as excess risk for CVD and particularly coronary heart disease.[124,125] Therefore, the more pronounced age-related cardiovascular risks seen in postmenopausal compared to premenopausal women and similarly aged men appear less likely due to an abrupt withdrawal of endogenous sex steroids during the ‘menopausal transition’, and more likely related to a progressive accumulation of hormone mediated

effects that begin in early adulthood, accelerate in midlife, and culminate in late life. This framework for considering ovarian aging effects of the cardiovascular system is aligned with the observed steadily progressing subclinical myocardial and vascular changes in aging women that begin their course decades prior to the menopausal transition and then, later on, further increase in rate of development.

The longitudinal perspective of ovarian aging is also potentially helpful for considering why most trials of exogenous hormone replacement therapy after menopause have shown no reduction in either subclinical or overt CVD outcomes.[126-129] Notwithstanding the effects of cumulative estrogen deficiency, conventional approaches to hormone replacement therapy may represent a mismatch of dosage and timing that may or may not be resolved by future studies.[130-132] Therefore, at present, there remains clinical equipoise around hormone therapies.[133] Relatedly, there remains a lack of clarity regarding the complex inter-related influences of general somatic aging, ovarian aging, and cardiovascular risk.[110,134] While ovarian aging can promote the development of subclinical and then clinical myocardial and vascular disease, cardiovascular risk may also predispose to ovarian aging (e.g. atherosclerosis involving microvasculature of the ovaries),[135] and age-related somatic mutations can affect both.[136,137]

Notably, additional approaches to clarifying hormone-related cardiovascular risk can involve examining the relative effects of sex-determining hormones in gender-affirming hormone therapy within transgender populations. Early data suggest that transgender females experience increased thromboembolic disease, whereas transgender males develop lipid profiles reflecting their gender rather than natal sex potentially without adverse cardiovascular risk.[138,139] Further longitudinal and outcomes studies are needed to improve our understanding of the interaction between sex-determining hormones and the aging trajectory.[140,141]

Conclusion

Over the past two decades, tremendous progress has been made in unveiling and clarifying age-based sex variation in cardiovascular phenotypes and outcomes. Evidence to date indicates that female-male differences in the development and progression of CVD arise from a combination of intrinsic, stochastic, and environmental factors influencing myocardial and vascular aging trajectories. In particular, intrinsic biological between-sex differences manifest as measurable relative dimorphism in cardiac and vascular structure and function, and this dimorphism sets the stage for the frequently observed sex divergent trajectories of response to cardiovascular risk exposures over the life course. The accumulating body of data suggests that sex differences in cardiovascular risk should be accounted for in all clinical trials and in a manner that also accounts for the differing trajectories of risk in women. It is possible that trials that deliberately include younger female populations and address risk factor modifications at an earlier age may reveal previously unforeseen benefits in the management of CVD in women. Together with ongoing work to investigate sex-based variation in cardiovascular risks across the lifespan, these broadened approaches promise to further our understanding of how to better mitigate potentially adverse sequelae of cardiovascular aging in both sexes.

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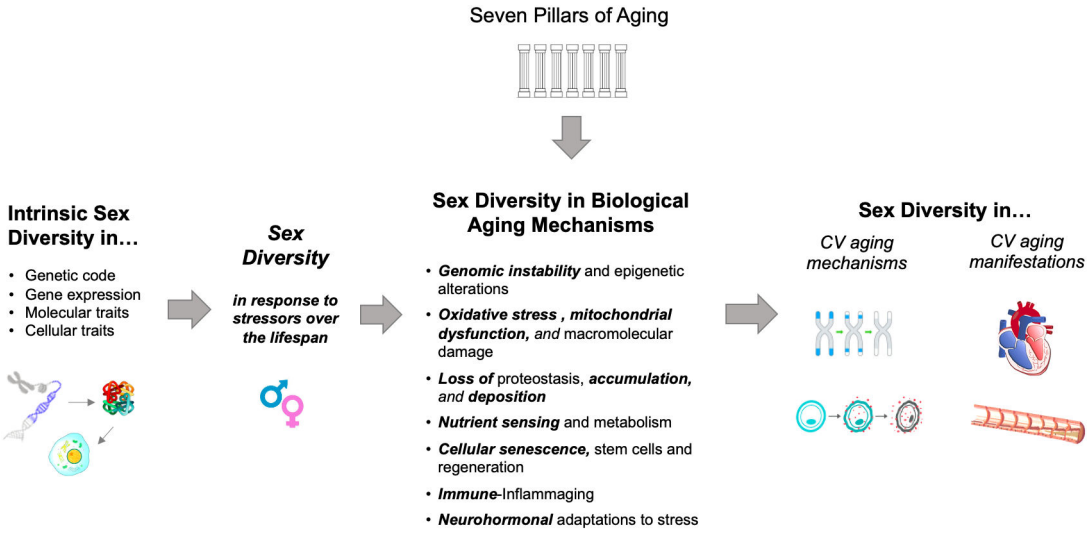

Figure 1.

Conceptual Overview of Sex-Based Variation in Mechanisms and Manifestations of Cardiovascular Aging

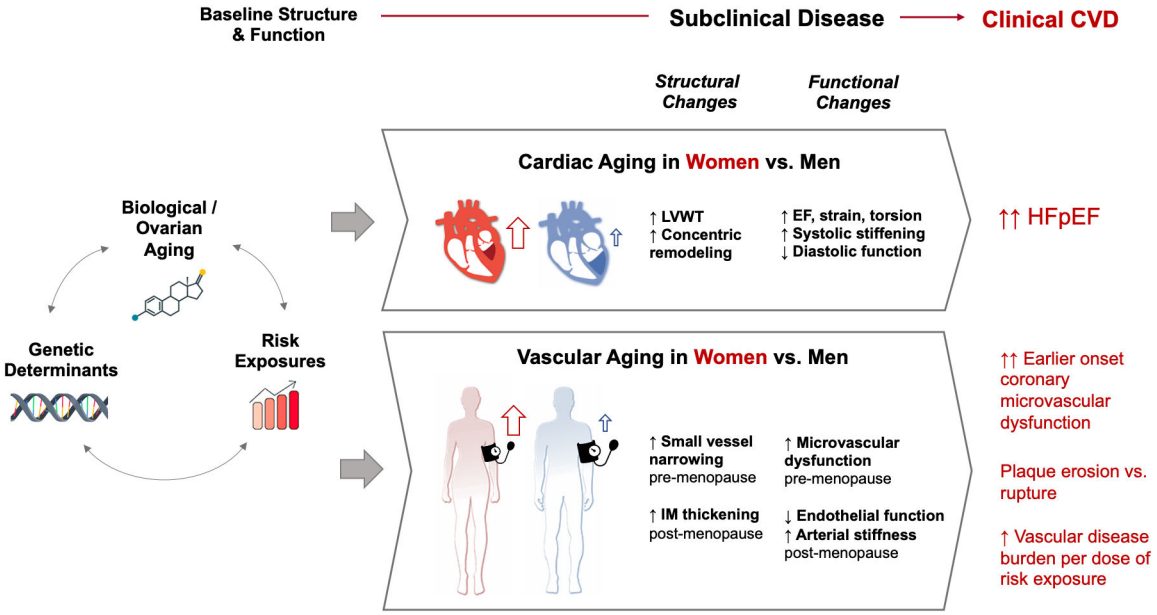

Figure 2.
Overview of Female-Predominant Cardiovascular Aging Phenotypes

Table 1.

Sex Differences in Cardiovascular Aging Mechanisms and Phenotypic Manifestations

	Cardiovascular Aging Mechanism		Cardiovascular Aging Manifestation	
	Female	**Male**	**Female**	**Male**
Cardiac	↑ Cardiac collagen accumulation * ↑Fibroblast activity ↑Reactive interstitial fibrosis ↓ Myocyte loss (−) autophagy and cellular turnover (−) stem cell regeneration (−) telomere shortening (−) aging miRNA expression ↑ Post-cardiac injury inflammatory transcriptome * ↓ Estradiol protection from ischemia/reperfusion injury * ↓ Estrogenic protection of reactive oxygen species	↑ Myocyte loss ↑autophagy, necrosis, and apoptosis ↓ stem cell regeneration Different fibroblast secretomes Different valvular interstitial cell expression profiles Higher somatic mutation accumulation rate in DNA Earlier immune aging Decreased mitochondrial lifespan ↓ Connexin expression in atrial myocytes	↑ Wall thickening in response to risk exposures ↑ MV leaflet thickening, prolapse, calcification risk ↑ Systolic torsion, LV shortening, LVEF ↑ LV end-systolic elastance ↑ Concentric remodeling ↑ Diastolic dysfunction Pre-clinical & clinical HFpEF phenotype	↑ AV calcification risk ↑ Bradyarrhythmia risk ↑ Eccentric remodeling ↑ Systolic dysfunction Pre-clinical & clinical HFrEF phenotype
Vascular	↑ sensitivity to cardiometabolic risk factors * ↑ Endothelial dysfunction * ↑Oxidative stress ↑Inflammation trajectory ↑ROS production ↑Nitric oxide suppression ↓ Vascular permeability to PDE3 inhibitor *[142] ↓ Anti-inflammatory macrophage protection with age * ↑ Salt sensitivity with age * ↓ Estrogenic vasodilation post-menopause *[70] ↑ Perivascular fibrosis * ↓ Baroreflex sensitivity ↑ Mineralocorticoid receptor expression[51]	(−) sensitivity to cardiometabolic risk factors ↑ No. endothelial cells Differential immune cell migration marker expression (↑VCAM-1) ↑ Macrophage adrenergic receptor expression ↓ Carotid wall shear stress ↑ Pulse wave velocity ↓ Acetylcholine response	Accelerated arterial stiffness Accelerated plaque formation in aging Accelerated incident hypertension with age ↑ ↑ Coronary microvascular dysfunction Accelerated renal dysfunction Coronary events shift from erosion-based to rupture-based with aging ↑ Multi-vessel peripheral arterial disease	Stable progressive aging trajectory Elevated morbidity and mortality due to long-term exposure to risk factors, chronic vascular lipid accumulation Coronary events more likely to be rupture-based from early age Earlier presentation of myocardial infarction ↑ Aortic aneurysm formation ↑ Aortic dissection risk

* Trajectory change associated with advancing age and/or estrogen decline

Table 2.

Major Findings from Observational Studies and Randomized Trials

Study ID	Sample Size	Setting	Age (Median, Mean, or age range)	Major Finding Relevant to CV Aging in Women Compared to Men
Observational studies				
32594163	3754	Patients undergoing coronary angiography	60	Concentric remodelling ↑ Eccentric hypertrophy ↓
16203909	2042	Community-dwelling	62	Age-related Ventricular-Vascular Stiffening ↑
20660804	4062	Framingham heart study	45	Age-associated increase in LV wall thickness ↑
27280886	8410	Asymptomatic participants	50	Age-related increase in LV wall thickness, LV mass index, and NT-proBNP ↑
16567580	2618	Dallas Heart Study	45	Left ventricular ejection fractions ↑
32506162	1367	Patients underwent positron emission tomography (PET)	63	Left ventricular ejection fractions (EF) ↑ EF>=65% is associated with MACE in women, but not in men.
23742210	5307	Subjects with normal echocardiography studies.	~40	Age-related increase in LV ejection fraction, LV fractional shortening and LV muscle mass index ↑
23147172	1478	MESA	65	Myocardial torsion ↑
23871886	1231	MESA	67	Potentially protective β-adrenergic effect ↓
19706861	136247	Patients with acute coronary syndrome	60-69	Women with STEMI had higher 30-day mortality ↑
24574260	279	HFpEF patients	71	Pronounced diastolic dysfunction to HFpEF ↑
30007554	22681	Community-based cohorts	60	Association of BMI with HFpEF versus HFrEF ↑
26404197	1552	Patients with nonobstructive CAD	51	Coronary microvascular abnormalities ↑
20579539	189	Women with suspected ischemia undergoing coronary angiogram	55	Association of Coronary microvascular reactivity to adenosine with major adverse outcomes ↑
27511975	435	Stable coronary artery disease or acute coronary syndromes	62	Plaque erosion ↑ Cholesterol and calcium content ↓
32861960	790	Patients with revascularization of the iliofemoral arteries	68	Rupture-prone characteristics ↑
31983726	1021	Patients underwent OCT of culprit lesions	69	Thin cap fibroatheroma ↑
16365194	6110	MESA	62	CAC score ↓
32828763	1255	Patients with suspected CAD	60	Calcified plaque volume progression ↑
30586725	28,732	ARIC Study Community Surveillance	48	Annual incidence of AMI hospitalizations ↑
28329052	113,407	Patients hospitalized for ACS	68	STEMI annual incidence ↑
26302759	5606911420	CHD mortality rates	-	CHD mortality rates ↑

Study ID	Sample Size	Setting	Age (Median, Mean, or age range)	Major Finding Relevant to CV Aging in Women Compared to Men
13679479	1860	Patients with non-diabetic renal disease	52	Rate of renal disease progression ↑
31940010	32833	Community based cohorts	48	Blood pressure elevation ↑
21695075	30,372	Population-based cohorts	-	Blood pressure elevation ↑
32063062	32833	Community based cohorts	37	Cardiometabolic-risk related SBP elevation ↑
15123572	521	Framingham heart study	57	Progression in arterial stiffness ↑
32130922	80415	Participants in the health examinations	48-60	Progression in arterial stiffness ↑
33486987	2026	Asklepios study	38	Progression in arterial stiffness ↑
10334811	89	Healthy subjects	49	Sympathetic activity ↓ Parasympathetic activity ↑
15687139	51	Healthy adults	27-28	Tonic sympathoadrenal activity-related autonomic nervous system ↓
33587655	27 542	Community based cohorts	-	CVD risk associated with SBP levels ↑
10919931	1028	Healthy Children	6-12	Environmental and genetic factors may have different effects on serum cholesterol in girls and boys.
19389672	267	Healthy pupils	10	Sex differences of carotid intima-media thickness exist in pupils
Randomized Trials				
26551272 NCT01206062	9361	SBP of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes	68	Intensive versus standard blood pressure control resulted in 16% and 28% lower risk of major outcome in women and men respectively
20228401 NCT00000620	4733	SBP of 130 mm Hg with diabetes	62	Intensive versus standard blood pressure control did not result in significant benefit in diabetic women and men.
34491661 NCT03015311	9624	Patients with hypertension	66	Intensive versus standard blood pressure control resulted in 21% and 30% lower risk of major outcome in women and men respectively
18259011	863	Patients with hypertension	66	Women had less hypertrophy regression during long-term antihypertensive treatment.
32946164 NCT02887183	794	Patients with chronic HFrEF	66	In women with HFrEF, treatment with S/V was associated with significant NT-proBNP reduction, health status improvement and reverse cardiac remodelling.
31736337 NCT01920711	4896	Patients with heart failure with preserved ejection fraction	72	As compared with valsartan, sacubitril-valsartan seemed to reduce the risk of heart failure hospitalization more in women than in men.

Abbreviations: LV: left ventricular; MACE: Major adverse cardiac events; MESA: Multi-Ethnic Study of Atherosclerosis; STEMI: ST-segment elevation myocardial infarction; HFpEF: heart failure with preserved ejection fraction; BMI: body mass index; CAD: coronary artery disease; CAC: coronary artery calcium; ARIC: Atherosclerosis risk in the community study; AMI: acute myocardial infarction; CHD: coronary heart disease; CVD: cardiovascular disease; ACS: acute coronary syndrome; S/V: sacubitril valsartan.