Review

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Differences in Risk Factors for Coronary Atherosclerosis According to Sex

Hack-Lyoung Kim 💿

Division of Cardiology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

ABSTRACT

Interest in sex differences related to coronary artery disease (CAD) has steadily increased, and the risk factors for CAD show distinct sex differences. For women, cardiovascular risk increases significantly after menopause due to a decrease in estrogen levels. In older individuals, increased arterial stiffness results in a higher pulse pressure, leading to a more common occurrence of isolated systolic hypertension; these changes are more noticeable in women. While the incidence of diabetes is similar in both sexes, women with diabetes face a 50% higher relative risk of fatal coronary heart disease compared to men. Smoking significantly increases the risk of ischemic heart disease in women, particularly those who are younger. The decrease in estrogen in women leads to a redistribution of fat, resulting in increased abdominal obesity and, consequently, an elevated cardiovascular risk. Pregnancy and reproductive factors also have a significant impact on CAD risks in women. Additionally, disparities exist in medical practice. Women are less likely to be prescribed cardioprotective drugs, referred for interventional or surgical treatments, or included in clinical research than men. By increasing awareness of these sex differences and addressing the disparities, we can progress toward more personalized treatment strategies, ultimately improving patient outcomes.

Keywords: Atherosclerosis; Cardiovascular disease; Gender; Heart disease risk factors; Sex

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and morbidity worldwide.^{1,2} Numerous studies, such as the Framingham Cohort Study, have identified key factors that play a pivotal role in the onset and progression of CVD.^{3,4} These determinants include high blood pressure,⁵ diabetes,⁶ dyslipidemia,⁷ smoking,⁸ and obesity.⁹ Not only are these factors crucial in understanding the epidemiology of CVD, but they are also relevant in devising strategies for intervention. These traditional risk factors, with a well-established association with CVD, have been the cornerstone on which medical professionals set standards of care.¹⁰ By targeting these risks, primary and secondary prevention therapies aim to reduce the incidence and progression of CVD in patients.^{11,12}

Interest in sex differences in CVD has been steadily growing. Numerous studies have revealed distinct differences between men and women in CVD incidence, risk factors, diagnostic and

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Correspondence to

Hack-Lyoung Kim

Division of Cardiology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, 5 Boramae-ro, Dongjak-gu, Seoul 07061, Korea.

Email: khl2876@gmail.com

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ORCID iDs

Hack-Lyoung Kim D https://orcid.org/0000-0002-6703-1472

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therapeutic approaches, and outcomes.¹³⁴⁵ Acknowledging and comprehending these sex differences in CVD is crucial for delivering holistic and individualized care. This recognition leads to improved clinical outcomes, more efficacious public health initiatives, and a deeper understanding of the disease's fundamental processes.¹⁴

This review discusses the differences between men and women regarding risk factors for coronary atherosclerosis. The first section primarily addresses traditional risk factors, while the latter explores non-traditional and women-specific risk factors. A section on sex disparities has also been incorporated toward the conclusion.

INCREASED CVD RISK IN MENOPAUSAL WOMEN

Metabolic syndrome is a constellation of traditional risk factors, and its prevalence differs between men and women. Based on national data, the prevalence of metabolic syndrome in men starts to increase in their 20s, peaks between the ages of 50 and 60 and subsequently decreases, whereas in women, the prevalence continues to rise with age.¹⁶ A parallel trend has been noted for the incidence of myocardial infarction and stroke in Korea.¹⁷ A study in the Netherlands analyzed 8,419 community residents, all over 55 and without preexisting CVD. It found that the risk of developing CVD increased sharply with age in elderly women, eventually equaling the total lifetime risk observed in men.¹⁸ An analysis of the results of the Framingham Cohort Study revealed that concomitant risk factors accounted for 40.3% of the impact of age on CVD in women, whereas this proportion was 11.9% in men.¹⁹ In an aging society, the prevalence of CVD in older women represents a substantial burden, incurring significant medical and societal costs.²⁰

The increased cardiovascular risk observed in elderly women can primarily be attributed to decreased blood estrogen levels. Estrogen exerts robust protective effects on the cardiovascular system by inhibiting fibrosis, promoting angiogenesis, exhibiting anti-oxidant and anti-inflammatory properties, stimulating nitric oxide production, and preserving endothelial cell function (**Fig. 1**).^{21:24} Low estrogen levels are associated with increased accumulation of visceral fat, insulin resistance, hyperglycemia, and chronic inflammation, all of which contribute to a higher prevalence of central obesity, hypertension, diabetes mellitus, and dyslipidemia in older women (**Fig. 2**).^{25:27} Therefore, post-menopause, the absence of estrogen in women's blood may expose them to heightened cardiovascular risk. Indeed, multiple clinical studies have demonstrated an inverse correlation between the length of exposure to endogenous estrogen and the incidence of cardiovascular events and mortality.^{28,29}

SEX DIFFERENCES IN CORONARY ATHEROSCLEROSIS

When analyzing patients undergoing invasive coronary angiography, distinct sex differences emerge in the manifestation of coronary artery disease (CAD). Men typically present with CAD at a younger age than women, and obstructive CAD is more prevalent in men.^{30,31} Men generally have a higher prevalence and greater extent of coronary plaque burden than women.³² This difference is particularly noticeable in younger age groups. Women often have more diffuse and less obstructive plaque, which complicates the diagnosis due to its subtler angiographic presentation.³³ Men are more likely to have calcified and fibrous plaques,





Fig. 1. Cardiovascular protective effects of estrogen.



Fig. 2. Mechanisms of how cardiovascular risk increases in postmenopausal women.

whereas women often have more fibro-fatty and mixed plaques.³² Additionally, microvascular dysfunction, in which myocardial ischemia occurs without significant stenosis of the epicardial coronary artery, is more common in women than in men.³⁴ Spontaneous coronary artery dissection, a noteworthy condition that involves tearing of the coronary artery wall, is significantly more common in women.³⁵ These conditions add a layer of complexity to cardiovascular diagnoses in female patients. Women are more likely to experience plaque erosion without concurrent coronary artery calcification. This characteristic is crucial as it influences the diagnostic process; in women, smaller blood vessels and a smaller necrotic core are common, rendering the coronary artery calcium (CAC) score less predictive of cardiovascular events than it is in men.³⁶ Estrogen plays a significant role in these sex differences, particularly through its protective effect against coronary artery calcification.³⁶ As a result, elevated CAC is a rare finding in younger women but becomes more common with advancing age, especially post-menopause, when the protective effects of estrogen are



diminished. This variation emphasizes the importance of sex-specific considerations in the evaluation and management of CAD.

TRADITIONAL RISK FACTORS

1. Hypertension

As individuals age, regardless of sex, systolic blood pressure tends to increase while diastolic blood pressure decreases.³⁷ The increase in diastolic blood pressure until the age of 50 is attributed to elevated peripheral resistance, while the subsequent decrease in diastolic blood pressure is linked to increased stiffness in the large arteries. These changes, compounded by the effects of menopause, contribute to accelerated vascular aging and atherosclerosis in elderly women.³⁸ Age-related vascular changes typically manifest as endothelial dysfunction and enhanced arterial stiffness, resulting in increased systolic blood pressure and pulse pressure. Notably, vascular aging initiates at an earlier age in men, but its progression is more rapid in women post-menopause.³⁹ Menopause is associated with a decrease in the estrogen-to-testosterone ratio, which results in endothelial dysfunction and elevated levels of angiotensin II. Concurrently, endothelial dysfunction triggers a decline in nitric oxide and an increase in endothelin, which contributes to heightened oxidative stress. These factors may lead to renal vasoconstriction, inducing hypertension in menopausal women.⁴⁰ Although some results have indicated that the risk of CVD at equivalent blood pressure levels is more pronounced in women than in men,^{41,42} overall, the cardiovascular risk due to high blood pressure seems to be similar in men and women.43

2. Diabetes mellitus

The overall incidence of diabetes is similar in both sexes, but the relative risk for CVD caused by diabetes mellitus is higher in women than in men. A meta-analysis of 37 prospective studies revealed that women with type 2 diabetes experienced a 50% higher incidence of fatal coronary heart disease than men with type 2 diabetes.⁴⁴ Another meta-analysis of 26 studies showed that women with type 1 diabetes had a roughly 40% greater excess risk of all-cause mortality, and twice the excess risk of fatal and nonfatal vascular events, compared with men with type 1 diabetes.⁴⁵ In one study analyzing heart failure patients, the prognostic value of diabetes was confirmed only in women.⁴⁶

While the precise cause of sex differences in diabetes risk remains unclear, it may be attributed to the fact that women with diabetes exhibit higher cardiovascular risk profiles than men with diabetes,⁴⁷ and are less frequently prescribed cardiovascular protective drugs, such as antiplatelets and statins.⁴⁸ There may also be inherent biological differences between men and women that influence cardiovascular risk, including differences in sex hormones and their effects on lipid metabolism, inflammation, and vascular response. It has been suggested that the cardioprotective effects of estrogen are weakened by diabetes mellitus, which disturbs ovarian aromatase activity that converts androgen into estradiol in the ovary.⁴⁹

The sex differences in the cardiovascular risks of diabetes emphasize the importance of personalized, sex-specific approaches in the management and treatment of diabetes and its associated cardiovascular risks. The higher relative risk experienced by women highlights the need for intensive cardiovascular risk factor management in women.



3. Dyslipidemia

Women have higher levels of high-density lipoprotein (HDL) cholesterol,⁵⁰ which is generally protective against CVD, than men.⁵¹ Men tend to have higher levels of smaller and denser low-density lipoprotein (LDL) particles,⁵² which are associated with increased cardiovascular risk.⁵³ Before menopause, women generally have a more favorable lipid profile than men of the same age, which is partly attributed to the protective effects of estrogen.⁵⁴ After menopause, women experience unfavorable changes in their lipid profiles, including increases in LDL cholesterol and decreases in HDL cholesterol, leading to a rise in cardiovascular risk that often surpasses the risk in men of the same age.^{55,56} Women with dyslipidemia, especially postmenopausal women, may have a higher risk of certain types of cardiovascular events, such as stroke, than men with similar lipid levels.⁵⁷ Generally, there are still insufficient data regarding the significance of sex differences in cardiovascular risk associated with dyslipidemia. Evidence suggests that women with dyslipidemia are less likely to receive lipid-lowering treatment and may also be less likely to achieve target lipid levels than men.^{58,59}

4. Smoking

Women smokers have a higher relative risk for coronary heart disease than men.⁶⁰⁻⁶³ The mechanisms behind this heightened risk are not entirely understood, but they are likely multifactorial, involving biological, physiological, and social factors. Smoking inhibits the cardiovascular-protective effects of estrogen or its production in women,^{64,65} potentially leading to more significant arterial damage and a higher risk of atherosclerosis. Although atherosclerotic plaques develop and blood clots form due to smoking similarly in both men and women, some argue that the incidence of arteriosclerotic CVD is higher in women because of their smaller arterial luminal diameter compared to men.⁶⁶ Additionally, when women smoke, their HDL cholesterol concentration decreases more than in men, which can also increase cardiovascular risk.⁶⁷ The higher prevalence of vasospasm, vasculitis, coronary dissection, and plaque erosion in women.^{62,68}

There are indications that women may be more adversely affected by secondhand smoke than men, potentially facing a higher relative risk of developing CVD from passive smoking.^{69,70} Both men and women substantially benefit from quitting smoking, which leads to a significant reduction in cardiovascular risk.^{71,72} However, some studies suggest that women may find it more challenging to quit smoking than men and might benefit from sex-specific smoking cessation strategies.⁷³ There may be differences in how men and women respond to interventions for smoking cessation, necessitating personalized and sex-specific approaches in some cases. Considering these sex-specific risks and differences, personalized prevention and intervention strategies considering sex may be necessary for effectively addressing smoking-related cardiovascular risks.

5. Obesity

Obesity is a major problem worldwide, as the number of obese people continues to increase and the mortality and morbidity rates due to obesity are high.⁷⁴ The correlation between obesity and elevated cardiovascular risk is well-established for both sexes.⁹ However, when assessed separately, the risk associated with obesity is slightly higher for men than for women.^{9,75} This difference is primarily attributed to the higher prevalence of abdominal obesity in men and the predominance of subcutaneous fat accumulation in women; these patterns are influenced by sex hormones.^{76,77} Abdominal obesity elevates cardiovascular risk



more due to the release of more toxic cytokines and a heightened inflammatory response from visceral adipose tissue compared to subcutaneous tissue.^{78,79} Post-menopause, women experience estrogen deficiency, leading to a redistribution of body fat that results in increased abdominal obesity, thereby elevating cardiovascular risk to levels comparable to men.⁸⁰⁻⁸² The surge in abdominal obesity in post-menopausal women is noteworthy, underscoring the need for tailored interventions and preventive measures for both sexes at different life stages to mitigate the associated risks effectively. It is crucial to have a sex-specific understanding and approach to managing the escalating obesity rate and its consequences in diverse populations.

To summarize the sex differences observed in cardiovascular risk stemming from traditional risk factors: it appears that no substantial differences exist between men and women with regards to hypertension and dyslipidemia. However, the risk associated with obesity is marginally higher in men than in women. Conversely, the risks posed by diabetes and smoking are significantly higher in women than in men.⁴³ These observations underscore the necessity for a sex-specific approach to assess cardiovascular risks effectively.

NON-TRADITIONAL RISK FACTORS

Non-traditional risk factors play a meaningful role in the development of CVD. Notably, approximately 15%–20% of individuals who experience myocardial infarction do not exhibit traditional risk factors.⁸³ Non-traditional cardiovascular risk factors include reproductive factors, chronic inflammation, emotional stress, and socioeconomic status.²⁰ Intriguingly, distinct sex differences in cardiovascular risk emerge among these non-traditional factors. As detailed above, estrogen depletion is a significant non-traditional cardiovascular risk factor in women. Reproductive factors will be discussed in more detail in the next section. It is markedly more common for women than men to have CVD affected by autoimmune conditions, rheumatic diseases, or psychosocial influences.⁸⁴ Chronic inflammation stemming from autoimmune or rheumatic diseases raises cardiovascular risk by inducing atherosclerosis, oxidative stress, and endothelial dysfunction due to vessel wall injuries.85,86 It is also important to know that radiation therapy used to treat breast cancer increases the risk of developing CAD in women.⁸⁷ Moreover, women are more susceptible than men to depression, a condition closely linked to elevated CVD risk.88 Chronic stress, whether from occupational, personal, or other causes, also exhibits sex differences in its effects on cardiovascular health. Chronic stress elevates CVD risk by triggering the sympathetic nervous system, promoting inflammation and endothelial dysfunction, influencing poor health behaviors, and exacerbating existing risk factors.⁸⁹ Chronic stress also affects platelet activation, contributing to thrombus formation.⁹⁰ Although some inconsistent findings have been reported,⁹¹ chronic stress also appears to increase cardiovascular risk more in women than in men.^{92,93} A holistic approach to CVD prevention would entail understanding and addressing these non-traditional risk factors while also managing the traditional ones, aiming to comprehensively diminish the overall CVD burden.

REPRODUCTIVE FACTORS

Reproductive factors play a crucial role in influencing CVD, especially in women. Early menopause, marked by reduced exposure to endogenous estrogen, is linked to a heightened CVD risk.^{28,29} Polycystic ovary syndrome often coincides with cardiovascular risk factors,



including hypertension, diabetes, and dyslipidemia, elevating the risk of CVD.⁹⁴ Conditions such as hypertensive disorders of pregnancy and gestational diabetes not only pose immediate risks, but also have long-term cardiovascular implications for women, persisting post-delivery.⁹⁵ Furthermore, preterm birth and low birth weight have been associated with increased maternal cardiovascular risk.^{96,97} Interestingly, even in uncomplicated pregnancies, having numerous childbirths (around 4–5 or more) can significantly amplify the risk of CVD.⁹⁸ The positive relationship between the number of pregnancies and organ damage was also confirmed in a study conducted in South Korea.⁹⁹⁴⁰¹ This is attributed to the cumulative physical stress, metabolic changes, and potential weight gain associated with repeated pregnancies.¹⁰²

Preeclampsia, a hypertensive disorder of pregnancy, is associated with an increase in cardiovascular risk that is thought to be comparable to, or even surpass, that of major established cardiovascular risk factors.^{103,104} In clinical practice, reproductive factors are frequently overlooked, yet they should be acknowledged as significant contributors to CVD in women. It is imperative to accurately identify these factors, incorporate them into diagnostic and therapeutic strategies, and optimize the cardiovascular outcomes for affected individuals.¹⁰⁵

Women's cardiovascular risk factors are shown in **Fig. 3**. Sex differences in the risk factors for coronary atherosclerosis are summarized in **Table 1**.

SEX DISPARITY IN RISK FACTOR CONTROL

It has been suggested that up to 80% of premature heart disease and stroke is preventable through a healthy diet, regular physical activity, and avoiding tobacco smoke.¹⁰⁶ From a primary prevention perspective, lifestyle interventions and education are paramount.¹⁰ However, adherence to these lifestyle recommendations is difficult in practice. According to statistics from the Korea Disease Control and Prevention Agency, there has been little improvement in smoking rates and physical activity levels in recent years. Additionally, the



Fig. 3. Cardiovascular risk factors in women.

LV, left ventricular; PCOS, polycystic ovary syndrome; PIH, pregnancy induced hypertension.



Table 1. Summary of sex differences in risk factors for coronary atherosclerosis

Risk factors	Sex-related characteristic
Age	Cardiovascular risk rises sharply in women post-menopause, making them more susceptible to cardiovascular diseases with age than men.
Hypertension	In elderly women, the rise in pulse pressure attributed to increased arterial stiffness is more pronounced than in elderly men. However, the effect of hypertension on the development of cardiovascular disease is comparable between both sexes.
Diabetes mellitus	The incidence of diabetes is comparable between men and women; however, women have a 50% greater risk of developing ischemic heart disease due to diabetes than men.
Dyslipidemia	Although there has been debate, the risk of developing cardiovascular disease due to dyslipidemia is similar for both men and women.
Smoking	Smoking has a more detrimental effect on women's cardiovascular system than men's. It is one of the primary risk factors for ischemic heart disease in women. Women smokers experience their first myocardial infarction significantly earlier than male smokers do.
Obesity	In men with pronounced abdominal obesity, the cardiovascular risk linked to obesity is somewhat higher than in women. However, for women, the cardiovascular risk associated with obesity rises with increasing abdominal obesity after menopause.
Non-traditional risk factors	Chronic inflammation, emotional stress, and socioeconomic status have a greater influence on the cardiovascular system in women than in men.
Reproductive factors	Hypertensive disorders of pregnancy, gestational diabetes, polycystic ovary syndrome, preterm delivery, low birth weight, multiparity (>3), and menopausal age are associated with cardiovascular risk in women.

management of high blood pressure and dyslipidemia has stagnated, with control rates not even reaching 50%.¹⁰⁷ Pharmacotherapy should be considered when the desired outcomes are not achieved through dedicated lifestyle interventions. While there might be minor variations among drugs, their efficacy in preventing CVD is generally understood to be consistent between men and women. Interestingly, with drugs such as angiotensin-converting enzyme inhibitors¹⁰⁸ and statins,¹⁰⁹ the improvement in cardiovascular outcomes appears marginally more pronounced in women than in men. Consequently, sex should not be a deterrent; cardiovascular medications should be promptly prescribed when appropriate.

Numerous studies indicate that women are less likely to be prescribed drugs with cardiovascular-protective effects compared to men. This trend is evident not only in both primary and secondary prevention scenarios.¹¹⁰⁴¹² Several factors may explain this disparity: women, being generally smaller, often have higher blood concentrations of drugs, potentially leading to increased side effects. Additionally, many drug effectiveness studies have traditionally been male-centric, and factors such as women's lower socioeconomic status might influence prescription patterns.^{58,113415} The less frequent prescription of cardiovascular preventive drugs for women contributes to a lower success rate in achieving targeted risk factor control, consequently worsening cardiovascular outcomes for women.^{58,116} It's imperative that we prioritize women, and address the existing gap in drug prescription rates for preventing CVD in women.

FUTURE PERSPECTIVES

To effectively prevent CVD, managing its risk factors is paramount. A thorough understanding of the disease is essential for accurate diagnosis and treatment. Notably, there are pronounced sex differences in CVD risk factors, which need to be comprehensively understood. For instance, both diabetes and smoking present heightened risks for women, necessitating intensified monitoring and treatment for female patients with these conditions. There is also a pressing need to recognize and address women-specific risk factors. Medical histories linked to menopause or pregnancy associated factors significantly affect women's cardiovascular health. Such information should be consistently collected



and integrated into standard medical practices. Alarmingly, women tend to be less adherent to cardiovascular preventive medications than men. Efforts must be intensified to boost medication compliance among women. Additionally, the existing sex gap in clinical evidence necessitates further research tailored to women's unique health challenges. An urgent task is to elevate awareness about heart diseases and associated risk factors in women.^{117,118} This is a pressing concern that demands immediate attention.

CONCLUSION

Sex differences significantly influence the effects of traditional risk factors on cardiovascular outcomes. Notably, diabetes mellitus and smoking have a more detrimental impact on women than on men. Additionally, women-specific risk factors, including autoimmune and rheumatic diseases, factors associated with pregnancy, and menopause, have a substantial effect on women's cardiovascular prognosis. Moreover, disparities exist between men and women in the utilization of cardiovascular medications for controlling these risk factors. Recognizing and addressing these sex differences and disparities is vital for improving cardiovascular outcomes in women.

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